STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 140013

TO: Andrew D Kosar
Location: rem/3c04/3c18
Art Unit: 1654
Tuesday, December 21, 2004

Case Serial Number: 10/068905

From: Deirdre Arnold
Location: Biotech-Chem Library
REM 1A64
Phone: 571-272-2532

Deirdre.Arnold@uspto.gov

Search Notes

- Packet 1: structure search (broader than the claim to pick up more hits)
- Packet 2: inventor search (beware of false hits on the names; records may duplicate hits from packet 1)

Please feel free to contact me if you have any questions or would like to amend the search.

(I am going on leave and will return on 12/28; if you need immediate assistance, please contact my supervisor Mary Hale.)

Thank you for using STIC services.

Regards,
Deirdre Arnold

Access DB# 140013

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: **Andrew D. Kosar** Examiner# : **80341** Date: **12/10/04**

Art Unit: **1654** Phone Number: **(571)272-0913** Serial Number: **10/068,905**

Mail Box and Bldg/Room Location: **Mail: REM 3c18** Results Format Preferred (circle): **Paper** Disk E-mail
Office: REM 3c04

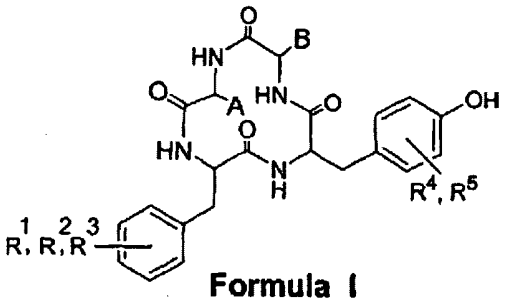
If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Histogranin-like peptides and non-peptides, processes for their preparation and uses thereof.
Inventors (please provide full names): Simon Lemaire, Irnma Bernatchez-Lemaire, Hoang-Than Le.
Earliest Priority Filing Date: filed in US 2/7/02, no foreign priority.
For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the following compound:



Formula I

A is hydrogen, -(C_1-C_8)alkyl or -(C_1-C_8)alkyl substituted by hydroxy;

B is -(C_1-C_6)alkylguanidino, -(C_1-C_6)alkyl(4-imidazolyl), p-aminophenylalkyl(C_1-C_6)-, -(C_1-C_6)alkylamino, p-guanidinophenylalkyl(C_1-C_6)- or 4-pyridinylalkyl(C_1-C_6)-;

R^1, R^2 and R^3 are, independent of one another, -hydrogen, -arylcarbonylamino, -(C_1-C_6)alkoylamino, -(C_1-C_6)alkylamino, -(C_1-C_6)a1kyloxy, -(C_1-C_6)alkylaminocarbonyl, -carboxy, -OH, -benzoyl, -p-halogenobenzoyl, -methyl, -S-(2,4-dinitrophenyl), -S-(3-nitro-2-pyridinesulfenyl), -sulfonyl, -trifluoromethyl, -(C_1-C_6)alkylaminocarbonylamino, -halo or -amino;

R^4 and R^5 are, independent of one another, -hydrogen, -(C_1-C_6)a1kyl, -methyloxy, -nitro, -amino, -arylcarbonylamino, -(C_1-C_6)alkoylamino, -(C_1-C_6)alkylamino, -halo or -OH.

The compound is effectively a cyclic tetrapeptide. Related compounds are in US 6,566,327.

****

STAFF USE ONLY

Searcher: Arnold
Searcher Phone: 2-2533
Searcher Location:
Date Searcher Picked Up: 12/13/04
Date Completed: 12/13/04
Searcher Prep & Review Time:
Clerical Prep Time:
Online Time:

Type of search

NA Sequence (#)
AA Sequence (#)
Structure (#)
Bibliographic
Litigation
Full Text
Patent Family
Other

Vendors and cost where applicable

STN
Dialog
Questel/Orbit
Dr. Link
Lexis/Nexis
Sequence System
WWW/Internet
Other (specify)

=> fil hcap

FILE 'HCAPLUS' ENTERED AT 10:01:26 ON 21 DEC 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 21 Dec 2004 VOL 141 ISS 26
FILE LAST UPDATED: 20 Dec 2004 (20041220/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil medlin

FILE 'MEDLINE' ENTERED AT 10:01:28 ON 21 DEC 2004

FILE LAST UPDATED: 20 DEC 2004 (20041220/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil biosis

FILE 'BIOSIS' ENTERED AT 10:01:31 ON 21 DEC 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 16 December 2004 (20041216/ED)

FILE RELOADED: 19 October 2003.

=> fil pascal

FILE 'PASCAL' ENTERED AT 10:01:34 ON 21 DEC 2004

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is prohibited without the prior written agreement of INIST-CNRS.

FILE LAST UPDATED: 13 DEC 2004 <20041213/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
IN THE BASIC INDEX (/BI) FIELD <<<

=> fil caba

FILE 'CABA' ENTERED AT 10:01:38 ON 21 DEC 2004

FILE COVERS 1973 TO 3 Dec 2004 (20041203/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

=> fil jicst

FILE 'JICST-EPLUS' ENTERED AT 10:01:41 ON 21 DEC 2004

FILE COVERS 1985 TO 20 DEC 2004 (20041220/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED
TERM (/CT) THESAURUS RELOAD.

=> fil confsci

FILE 'CONFSCI' ENTERED AT 10:01:44 ON 21 DEC 2004

FILE COVERS 1973 TO 18 Nov 2004 (20041118/ED)

=> fil embas

FILE 'EMBASE' ENTERED AT 10:01:48 ON 21 DEC 2004

FILE COVERS 1974 TO 17 Dec 2004 (20041217/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> fil drugu

FILE 'DRUGU' ENTERED AT 10:01:52 ON 21 DEC 2004

FILE LAST UPDATED: 8 DEC 2004 <20041208/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<

```
>>>  THESAURUS AVAILABLE IN /CT  <<<

>>>  A RECENT REVIEW OF PSYCHIATRIC DISEASE KEYWORDS USED
     IN DERWENT DRUG FILE HAS PROMPTED A REVISION BASED
     ON STANDARD TERMS USED IN DSM-IV (DIAGNOSTIC AND
     STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH
     EDITION).
     FOR FURTHER DETAILS:
http://thomsonderwent.com/derwenthome/support/userguides/lit_guide

=> fil wpix

FILE 'WPIX' ENTERED AT 10:01:55 ON 21 DEC 2004
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FILE LAST UPDATED:          16 DEC 2004      <20041216/UP>
MOST RECENT DERWENT UPDATE:     200481        <200481/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<

>>> NEW DISPLAY FORMAT HITSTR ADDED ALLOWING DISPLAY OF
    HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT  <<<

>>> SMILES and ISOSMILES strings are no longer available as
    Derwent Chemistry Resource display fields  <<<

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 10:01:59 ON 21 DEC 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Dec 17, 2004 (20041217/UP).

=>
     (FILE 'HCAPLUS, MEDLINE, BIOSIS, PASCAL, CABA, JICST-EPLUS, CONFSCI,
     EMBASE, DRUGU, WPIX' ENTERED AT 09:33:12 ON 21 DEC 2004)

=> d que l33
L24          977 SEA LEMAIRE, S?/AU
L25          407 SEA LEMAIRE, I?/AU
L26            3 SEA BERNATCHEZ-LEMAIRE, I?/AU
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L27           0 SEA BERNATCHEZ, I?/AU
L28        6756 SEA LE, H?/AU
L29         119 SEA ?HISTOGRANIN?
L30          89 SEA (L24 OR L25 OR L26 OR L27 OR L28) AND L29
L31          32 DUP REM L30 (57 DUPLICATES REMOVED)
L32      244793 SEA ?OTTAWA?/PA,CS,SO
L33          27 SEA L31 AND L32


=>

=> d ibib abs ed l33 1-
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS, PASCAL, DRUGU' - CONTINUE?
(Y)/N:y


YOU HAVE REQUESTED DATA FROM 27 ANSWERS - CONTINUE? Y/(N):y

L33  ANSWER 1 OF 27  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2004:292557  HCAPLUS
DOCUMENT NUMBER:         141:33318
TITLE:                   Histogranin-like antinociceptive and
                         anti-inflammatory derivatives of o-phenylenediamine
                         and benzimidazole
AUTHOR(S):               Le, Hoang-Thanh; Lemaire, Irma B.;
                         Gilbert, Annie-Kim; Jolicoeur, Francois; Yang, Lin;
                         Leduc, Natacha; Lemaire, Simon
CORPORATE SOURCE:        Department of Cellular and Molecular Medicine, Faculty
                         of Medicine, University of Ottawa,
                         Ottawa, ON, Can.
SOURCE:                  Journal of Pharmacology and Experimental Therapeutics
                         (2004), 309(1), 146-155
                         CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER:               American Society for Pharmacology and Experimental
                         Therapeutics
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Histogranin (HN)-like nonpeptides were designed and synthesized
     using benzimidazole (compound 1) and o-phenylenediamine (compds. 2-7) as
     scaffolds for the attachment of phenolic hydroxyl and basic guanidino
     pharmacophoric elements present in HN. The benzimidazole derivative
     N-5-guanidinopentanamide-(2R)-yl-2-(p-hydroxybenzyl)-5-
     carboxybenzimidazole (1) and the o-phenylenediamine derivative
     N-5-guanidinopentanamide-(2S)-yl-2-N-(p-hydroxyphenylacetyl)
     phenylenediamine (2) were more potent analgesics than HN in both the mouse
     writhing (5.5 and 3.5 as potent as HN, resp.) and tail-flick (11.8 and 8.0
     as potent as HN, resp.) pain assays. Improvements in the potencies and
     times of action of compound 2 in the mouse writhing test were obtained by
     attaching carboxyl (6) or ρ-Cl-benzoyl (7) groups at position 4 of the
     (2R) o-phenylenediamine derivative (5). In rats, compds. 2 (80 nmol i.t.), 6
     (36 nmol i.t.), and 7 (18 nmol i.t.) were effective in blocking both
     persistent inflammatory pain in the formalin test and hyperalgesia in the
     complete Freund adjuvant assay. Compds. 2, 6, and 7, but not compound 1 at
     10 nmol (i.c.v.) also mimicked the HN (60 nmol i.c.v.) blockade of
     N-methyl-D-aspartate (NMDA)-induced convulsions in mice. Finally, in
     primary cultures of rat alveolar macrophages, HN and compds. 1, 2, 6, and
     7 (10-8 M) significantly blocked lipopolysaccharide-induced
     cyclooxygenase-2 induction and prostaglandin E2 secretion. These studies
     indicate that both derivs. of benzimidazole and o-phenylenediamine mimic
     the in vivo antinociceptive and in vitro anti-inflammatory effects of HN,
```

but the HN protection of mice against NMDA-induced convulsions is mimicked only by the o-phenylenediamine derivs.

ED Entered STN: 09 Apr 2004
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:633749 HCAPLUS
DOCUMENT NUMBER: 139:180347
TITLE: Preparation of **histogranin**-like peptides and non-peptides
INVENTOR(S): **Lemaire, Simon; Bernatchez-Lemaire, Irma; Le, Hoang-Tanh**
PATENT ASSIGNEE(S): University of **Ottawa**, Can.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003066673	A1	20030814	WO 2003-CA148	20030205
WO 2003066673	C1	20031204		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003176329	A1	20030918	US 2002-68905	20020207
EP 1481002	A1	20041201	EP 2003-737222	20030205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-68905 A 20020207
WO 2003-CA148 W 20030205

OTHER SOURCE(S): MARPAT 139:180347
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to new basic amino acid derivs. I, II and III [A is H, alkyl, or hydroxyalkyl; B is guanidinoalkyl, 4-imidazolylalkyl, aminoalkyl, p-aminophenylalkyl, p-guanidinophenylalkyl, or 4-pyridinylalkyl; D is CO, CO-alkylene, or alkylene; E is a single bond or alkylene; Z is NH2, amino groups, OH, alkoxy, benzyloxy, or halobenzyl; R1-R5 are independently H or various substituents] and to their preparation and use in treatment of pain. The compds. have **histogranin**-like antinociceptive, morphine potentiating and COX-2 induction modulating activities. Thus, cyclo[Gly-(p-chloro)Phe-Tyr-D-Arg] (I-1) was prepared on an oxime resin using tert-butoxycarbonyl (Boc) protection and cleaved from the resin using intrachain aminolysis in the presence of AcOH and

diisopropylethylamine. I-1 showed AD50 = 0.17 nmol/mouse and an analgesic potency ratio of 135 relative to **histogranin** in a mouse writhing pain assay.
ED Entered STN: 15 Aug 2003
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:421338 HCAPLUS
DOCUMENT NUMBER: 139:133827
TITLE: Bioactive Peptidic Analogues and Cyclostereoisomers of the Minimal Antinociceptive **Histogranin** Fragment-(7-10)
AUTHOR(S): **Le, Hoang-Thanh**; **Lemaire, Irma B.**; Gilbert, Annie-Kim; Jolicoeur, Francois; **Lemaire, Simon**
CORPORATE SOURCE: Department of Cellular and Molecular Medicine, Faculty of Medicine, University of **Ottawa**, **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Journal of Medicinal Chemistry (2003), 46(14), 3094-3101
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:133827
AB Novel analogs of the minimal antinociceptive **histogranin** (HN) fragment Gly7-Gln8-Gly9-Arg10, in which amino acids in positions 8-10 were replaced by lipophilic amino acids and corresponding D-amino acid residues in combination with N- to C-terminal cyclization, were synthesized and tested in various animal models of pain. All synthetic peptides were potent and efficacious analgesics in the mouse writhing test. Cyclo[Gly-Ala-Tyr-D-Arg] (9) and cyclo[Gly-p-Cl-Phe-Tyr-D-Arg] (10) were the most potent analgesics, being 17 and 135 times as potent as HN, resp. (AD50 of 1.37 and 0.17 nmol/mouse icv, as compared with 23 nmol/mouse for HN). The times of action of compds. 9 and 10 were also much improved with half-maximal effects still being observed 60 min and >90 min after their administration, resp., as compared with 8.1 min for the parent peptide HN-(7-10) and 22.1 min for HN. At analgesic doses, compds. 9 and 10 were devoid of motor effect as assessed by the mouse rotarod assay. As already observed with HN, compds. 9 (10 nmol/rat; i.t.) and 10 (0.5 nmol/rat; i.t.) were effective in blocking persistent inflammatory pain in the formalin test and hyperalgesia induced by intraplantar administration of complete Freund adjuvant. In addition, the analgesic effects evoked by compds. 9 (10 nmol/mouse; icv) and 10 (1 μmol/kg; i.v.) in the mouse writhing test and compound 9 (10 nmol/mouse; icv) in the mouse tail flick assay were similarly antagonized by the dopamine D2 receptor antagonist raclopride (1 nmol/mouse; icv) but not the opiate antagonist naloxone (1 nmol/mouse; icv). Finally, the various cyclic peptides competed with the binding of [3H]raclopride in rat brain membrane prepns. Their ability to compete with the binding of the D2 ligand correlated well with their potency in alleviating pain in the mouse writhing test (r = 0.95). These results indicate that the analgesic activity of the minimal active core in HN can be improved by changes that favor its interaction with the dopamine D2 receptor.
ED Entered STN: 03 Jun 2003
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:76531 HCAPLUS
DOCUMENT NUMBER: 134:126140
TITLE: Interactions of **histogranin** and related peptides with dopamine D2 receptor in rat brain membranes
AUTHOR(S): Ruan, Hong; **Lemaire, Simon**
CORPORATE SOURCE: Department of Cellular and Molecular Medicine, Faculty of Medicine, University of **Ottawa**, **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Synapse (New York) (2001), 39(3), 270-274
CODEN: SYNAET; ISSN: 0887-4476
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Histogranin** (HN) and related peptides inhibit the binding of the D2 receptor ligand [3H]raclopride to rat brain membranes in dose- and structure-dependent manners. The interaction of the peptides with the D2 site is competitive and resembles that of D2 agonists. The D2 agonist-like binding potencies of HN and related peptides correlate well with their analgesic potencies in the mouse writhing test.
ED Entered STN: 02 Feb 2001
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:875421 HCAPLUS
DOCUMENT NUMBER: 134:66276
TITLE: Non-opioid antinociceptive effects of supraspinal **histogranin** and related peptides: possible involvement of central dopamine D2 receptor
AUTHOR(S): Ruan, H.; Prasad, J. A.; **Lemaire, S.**
CORPORATE SOURCE: Department of Molecular and Cellular Medicine, Faculty of Medicine, University of **Ottawa**, **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Pharmacology, Biochemistry and Behavior (2000), 67(1), 83-91
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antinociceptive effects of intracerebroventricular (ICV) administration of **histogranin** (HN) and related peptides were assessed in the mouse writhing and tail-flick assays. In the writhing test, the peptides displayed dose-dependent analgesic effects with an AD50 of 23.9 nmol/mouse for HN and the following order for other peptides: HN-(7-15) < histone H4-(86-100) ≈ HN ≈ HN-(7-10) < [Ser1]HN < osteogenic growth peptide (OGP) ≈ HN-(1-10). HN-(6-9) and HN-(8-10) did not show any significant analgesic activity at 50 nmol/mouse. The importance of the C- and N-terminal amino acids in the analgesic activity of the peptides was demonstrated by the prolonged effects of HN and [Ser1]HN (≈30 min) compared with those of HN fragments (HN-(7-15), HN-(1-10) and HN-(7-10): 5-10 min). The analgesic activity of [Ser1]HN (50 nmol/mouse) was not affected by the coadministration of opioid (naloxone, 1 nmol/mouse), NMDA (CPP, 0.3 and MK-801, 0.3 nmol/mouse) and D1 (SCH-23390, 0.5 nmol/mouse) receptor antagonists, but it was significantly antagonized by the coinjection of the D2 receptor antagonist raclopride (0.5 nmol/mouse). In the mouse tail-flick assay, HN and related peptides (50 nmol/mouse) also showed significant analgesic activity (15-35% MPE). The analgesic effect of [Ser1]HN was dose-dependent and, at 75 nmol/mouse, lasted for up to 45

min, and was partially blocked by the coadministration of raclopride (1 nmol/mouse), but not naloxone (2 nmol/mouse). In the mouse rotarod assay, relative high doses (75-100 nmol/mouse) of HN and related peptides did not significantly affect motor coordination. These results indicate that supraspinal administration of HN and related peptides induce significant non-opioid analgesic effects devoid of motor activity by a mechanism that involves the participation of central dopamine D2 receptors.

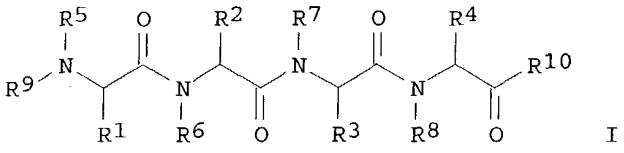
ED Entered STN: 14 Dec 2000
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:297437 HCAPLUS
DOCUMENT NUMBER: 130:297008
TITLE: Preparation of **histogranin** peptide analogs as analgesics
INVENTOR(S): **Lemaire, Simon**
PATENT ASSIGNEE(S): University of **Ottawa**, Can.
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9921877	A1	19990506	WO 1998-CA1002	19981026
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2219437	AA	19990424	CA 1997-2219437	19971024
CA 2224066	AA	19990424	CA 1998-2224066	19980224
CA 2306754	AA	19990506	CA 1998-2306754	19981026
AU 9897311	A1	19990517	AU 1998-97311	19981026
EP 1025119	A1	20000809	EP 1998-951127	19981026
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6566327	B1	20030520	US 2000-530123	20000706
US 2004006013	A1	20040108	US 2003-437435	20030514

PRIORITY APPLN. INFO.:			
CA 1997-2219437	A	19971024
CA 1998-2224066	A	19980224
WO 1998-CA1002	W	19981026
US 2000-530123	A3	20000706

OTHER SOURCE(S): MARPAT 130:297008
GI



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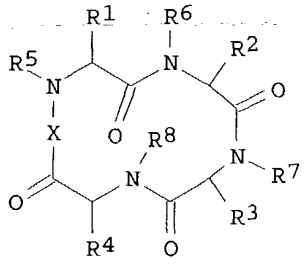
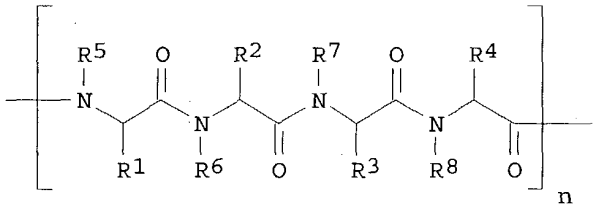


II

Q^2 = 

AB The invention relates to linear and cyclic **histogranin** peptide and pseudopeptide compds. I and II [R1 = H, alkyl, alkenyl, alkynyl, (CH2)nQ, Q = NH2, NHCH(NH)NH2, 4-imidazolyl, (un)substituted Ph, (un)substituted 3-indolyl; n = 0-10; R4 = = (CH2)nQ1, Q1 = NH2, NHC(:NH)NH2, 3-imidazolyl; R5, R9 = independently H, alkyl, alkenyl, alkynyl, alkylcarbonyl, aminocarbonyl, (CH2)n-aryl; R6-R8 = independently OH, alkoxy, alkenyloxy, alkynyloxy, amino, alkylamino, dialkylamino, alkylaryl, arylalkoxy, aryloxy, alkoxyaryl, A1, A1-A2, A1-A2-A3, A1-A2-A3-A4, A1-A2-A3-A4-A5; A1 = Thr, Ser; A2 = Leu, Gly, Ala, Val, Ile; A3 = Tyr, Phe, Trp; A4 = Gly, Ala, Leu, Ile, Val; A5 = Phe, Tyr, Trp; X = amino acid or peptide residue A1, A1-A2, A1-A2-A3, A1-A2-A3-A4; A1-A2-A3-A4-A5, peptide segment Q3; and pseudopeptide analogs thereof], and pharmaceutically acceptable salts and esters thereof, useful as analgesics, pharmaceutical compns. comprising such compds., the use of the compds. and the compns. in the treatment of pain, and com. packages containing such compds. and compns. Thus, cyclo(Gly-D-Gln-Tyr-D-Arg) (III) was prepared on an oxime resin using tert-butoxycarbonyl (Boc) protection and cleaved from the resin using intrachain aminolysis in the presence of AcOH and diisopropylethylamine. III showed AD50 = 4.41 nmol/mouse and an analgesic potency ratio of 10.6 relative to **histogranin** in a mouse writhing pain assay.

ED Entered STN: 14 May 1999

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:924339 HCAPLUS

TITLE: Synthesis and biological activity of **histogranin** and related peptides.

AUTHOR(S): Prasad, Jyoti; Shukla, V. K.; **Lemaire, S.**

CORPORATE SOURCE: University **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Book of Abstracts, 210th ACS National Meeting, Chicago, IL, August 20-24 (1995), Issue Pt. 2, MEDI-075. American Chemical Society: Washington, D. C.
CODEN: 61XGAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB **Histogranin** (HN) was first isolated from bovine adrenal medulla and shown to be a pentadecapeptide displaying N-methyl-D-aspartate (NMDA)-receptor antagonist activity. In order to determine the active pharmacophore of HN, fragments were synthesized and their structure-activity relationships studied by measuring their ability to displace the binding of [125I][Ser1]HN to rat brain membrane prepns. and to block NMDA-induced convulsions in mice. In the binding assay, only the full length peptide HN and HN-(1-10) displayed a high affinity (Ki of 72 and 162 nM, resp.). The least active peptide fragment tested was HN-(6-10)(Ki of 164 μM). In vivo, HN and HN-(2-15) (100 nmol, i.c.v.) produced 94 and 40% protection against NMDA-induced convulsions in mice, resp. None of the other peptide fragments displayed significant anticonvulsant activity. The protective activity of HN (60 at 100 nmol) was markedly antagonized by the coadministration of HN(1-10) (100 nmol). The results indicate that the in vivo anti-NMDA and in vitro binding activities of HN and related peptides, with the exception of HN(1-10) require the integrity of the mol. On the other hand, the high affinity of HN-(1-10), for HN binding sites corelates well with its antagonistic effects towards the activity of the parent peptide. (Supported by Ciba-Geigy/Medical Research Council Canada).

ED Entered STN: 16 Nov 1995

L33 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:559024 HCAPLUS
DOCUMENT NUMBER: 122:306685
TITLE: Synthesis and biological activity of **histogranin** and related peptides
AUTHOR(S): Prasad, Jyoti A.; Shukla, Vijay K.; **Lemaire, Simon**
CORPORATE SOURCE: Dep. Pharm., Univ. **Ottawa**, **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Canadian Journal of Physiology and Pharmacology (1995), 73(2), 209-14
CODEN: CJPPA3; ISSN: 0008-4212
PUBLISHER: National Research Council of Canada
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Histogranin** (HN) was first isolated from bovine adrenal medulla and shown to be a pentadecapeptide displaying N-methyl-D-aspartate (NMDA) receptor antagonist activity. To determine the active pharmacophore of HN, fragments of the peptide were synthesized and their structure-activity relationships studied by measuring their ability to displace the binding of [125I][Ser1]HN to rat brain membrane prepns. and to block NMDA-induced convulsions in mice. In the binding assay, only the full length peptide HN(1-10) displayed a high affinity (Ki of 72 and 162 nM, resp.). All other tested fragments with deletions at the N- and(or) C-terminals of the mol. showed large (16-2500-fold) decreases in potency. The least active peptide fragment tested was HN(6-10) (Ki of 164 μM). In vivo, HN and HN(2-15) (100 nmol; i.c.v.) produced 94 and 40% protection against NMDA-induced convulsions in mice, resp. None of the other peptide fragments displayed significant anticonvulsant activity. The protective activity of HN (60 and 100 nmol) was markedly antagonized by

coadministration of HN(1-10) (100 nmol). The results indicate that the in vivo anti-NMDA and in vitro binding activities of HN and related peptides, with the exception of HN(1-10), depend upon the integrity of the mol. The high affinity of HN(1-10) for HN binding sites correlates well with its antagonist effects towards the activity of the parent peptide.
ED Entered STN: 18 May 1995

L33 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:422139 HCAPLUS
DOCUMENT NUMBER: 122:205334
TITLE: **Histogranin**, a modified histone H4 fragment endowed with N-methyl-D-aspartate antagonist and immunostimulatory activities
AUTHOR(S): **Lemaire, Simon**; Rogers, Cheryl; Dumont, Michel; Shukla, Vijay K.; Lapierre, Chantal; Prasad, Jyoti; **Lemaire, Irma**
CORPORATE SOURCE: Dep. Pharm., Fac. Med., Univ. **Ottawa**, **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Life Sciences (1995), 56(15), 1233-41
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A minireview, with 34 refs. **Histogranin** is a naturally-occurring pentadecapeptide with a structure 80% homologous with that of fragment-(86-100) of histone H4. First isolated from bovine adrenal medulla, the peptide was also shown to be present in the pituitary, brain, adrenal glands, blood plasma, lungs and spleen. At the subcellular level, **histogranin** is concentrated in secretory vesicles and it is released from perfused bovine adrenal glands 15-35 min after stimulation with carbamylcholine as opposed to catecholamines and [Leu5]enkephalin which are released immediately after stimulation. Rat brain membranes possess specific binding sites for [125I][Ser1] **histogranin** with characteristics of a receptor, namely high affinity, saturability, reversibility and sensitivity to heat and proteolytic enzyme treatments. Intracerebroventricular injections of synthetic **histogranin** (10-100 nmol) in mice protect them against N-methyl-D-aspartate (NMDA)-induced convulsions without affecting convulsions induced by (R,S)-α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA), kainate and bicuculline. The peptide also binds to specific sites on human peripheral blood mononuclear cells and it evokes the release of tumor necrosis factor-α (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) from isolated rat macrophages in culture. Since the structure of histone H4 is considered as one of the most conservative, it is presumed that **histogranin** possesses its own precursor and that its gene is distinctly expressed.
ED Entered STN: 17 Mar 1995

L33 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:297048 HCAPLUS
DOCUMENT NUMBER: 122:72627
TITLE: N-Methyl-D-aspartate receptor antagonist activity and phencyclidine-like behavioral effects of the pentadecapeptide, [Ser1]**histogranin**
AUTHOR(S): Shukla, Vijay K.; **Lemaire, Simon**; Dumont, Michel; Merali, Zul
CORPORATE SOURCE: Faculty Medicine School Psychology, University **Ottawa**, **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Pharmacology, Biochemistry and Behavior (1995), 50(1), 49-54

CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The behavioral and pharmacol. profiles of [Ser1]**histogranin** ([Ser1]HN) were assessed by monitoring its ability to displace the binding of the specific N-methyl-D-aspartate (NMDA) receptor ligand, [3H]CGP 39653, to block the convulsant effects of NMDA and other excitatory agents in mice, and to produce phencyclidine (PCP)-like behavioral effects in rats. The peptide potently inhibited [3H]CGP 39653 binding to membrane prepns. of rat brain with an IC50 of 198 nM and a maximal inhibition of 34% of the specific binding activity. Saturation binding expts. with [3H]CGP 39653 in the absence and presence of [Ser1]HN (2 μM) indicated that the inhibitory effect of the peptide was noncompetitive, producing a decrease in the maximal number of binding sites (Bmax of 62.5 fmol/mg protein as compared with 91.3 fmol/mg protein in control), but no significant change in the affinity (Kd of 4.5 nM as compared with 5.1 nM in control). Intracerebroventricular (ICV) injection of [Ser1]HN (10-100 nmol) in mice evoked a dose-dependent and selective blockade of NMDA-induced convulsions. In rats, [Ser1]HN (2.5-100 nmol, ICV) produced dose-dependent stereotypy, ataxia, and locomotion similar to those observed with PCP, at doses ranging between 50 and 400 nmol. The data indicate that [Ser1]HN noncompetitively interacts with the NMDA receptor, an action that goes along with its in vivo NMDA receptor antagonist activity and PCP-like behavioral effects.
ED Entered STN: 14 Jan 1995

L33 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:628420 HCAPLUS
DOCUMENT NUMBER: 121:228420
TITLE: Up-regulation of cytokine production in alveolar macrophages by **histogranin**, a novel endogenous pentadecapeptide
AUTHOR(S): **Lemaire, I.**; Yang, H.; Cantin, M.-F.; **Lemaire, S.**
CORPORATE SOURCE: Fac. Medicine, Univ. **Ottawa**, **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Immunology Letters (1994), 41(1), 37-42
CODEN: IMLED6; ISSN: 0165-2478
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recently, **histogranin** (HN), a newly found pentadecapeptide, was shown to enhance tumor necrosis factor (TNF) production by alveolar macrophages (AM). The authors investigated whether HN was present in tissues rich with immune cells and further explored the effect of HN and [Ser1]HN on the production of TNF and other key cytokines. Relatively high levels of immunoreactive (ir)-HN were found in rat lung (14.9 pmol/g) and spleen (12.3 pmol/g), indicating its localization in close proximity to macrophages/monocytes and lymphocytes. Furthermore, HN and [Ser1]HN (10-8-10-7M) stimulated basal and lipopolysaccharide (LPS)-induced interleukin 1 (IL-1) mRNA expression and IL-1 release from rat AM. [Ser1]HN also stimulated basal and LPS-induced interleukin-6 (IL-6) release. Although HN did not affect the kinetics of cytokine production, the maximal enhancing effect of HN was seen at 3 h for TNF, 6 h for IL-1 and 18 for IL-6. These data indicate that HN can up-regulate a cytokine cascade involving TNF, IL-1 and IL-6 and suggest a role for this endogenous peptide in immune regulation.
ED Entered STN: 12 Nov 1994

L33 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:427526 HCAPLUS
DOCUMENT NUMBER: 121:27526
TITLE: Interaction of **histogranin** and related peptides with [3H]dextromethorphan binding sites in rat brain
AUTHOR(S): Dumont, Michel; Prasad, Jyoti; **Lemaire, Simon**
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, University of **Ottawa**, **Ottawa**, ON, K1H 8M5, Can.
SOURCE: Neuroscience Letters (1994), 173(1-2), 135-8
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Histogranin** (HN) and related peptides were tested for their ability to modulate the binding of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, [3H]dextromethorphan ([3H]DM), to rat brain membranes. HN, [Ser1]HN and the C-terminal fragment HN-(6-15) (0.1 nM-1 μM) potentiated (up to 1.6-fold) the binding of [3H]DM (5 nM) whereas the N-terminal fragment HN-(1-10) had no effect. The potentiation of [3H]DM binding by [Ser1]HN was blocked by NMDA (100 μM) and the NMDA receptor antagonist, CPP (1 μM) but not by the sigma (σ) receptor ligand, (+)-pentazocine (0.1 μM) and the phencyclidine (PCP) receptor ligand, TCP (1 μM). Equilibrium binding expts. in presence of TCP (1 μM) to block PCP receptors indicated that [Ser1]HN (1 μM) causes a significant increase in the binding capacity (Bmax) of [3H]DM (from 2.46 to 3.46 pmol/mg protein) but no change in the apparent dissociation constant (Kd
of 428 nM as compared with 487 nM). The results indicate that HN and related peptides specifically enhance the number of [3H]DM binding sites associated to the NMDA receptor complex.

ED Entered STN: 23 Jul 1994

L33 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:209476 HCAPLUS
DOCUMENT NUMBER: 120:209476
TITLE: Blockade of NMDA-induced potentiation of [3H]TCP binding to rat brain membranes by **histogranin**
AUTHOR(S): **Lemaire, S.**; Lapierre, C.; Skukla, V. K.
CORPORATE SOURCE: Dep. Pharmacol., Univ. **Ottawa**, **Ottawa**, ON, K1H 8MH, Can.
SOURCE: Regulatory Peptides (1994), (Suppl. 1), S271-S272
CODEN: REPPDY; ISSN: 0167-0115
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of **histogranin** and its chemical stable analog, [Ser1] **histogranin**, on NMDA-induced potentiation of [3H]-N-(1-[2-thienyl]-cyclohexyl)-3,4-piperidine ([3H]TCP) binding to rat brain membranes were studied. Both compds. at 1-10 μM produced a dose-dependent blockade of NMDA-induced potentiation of [3H]TCP binding to the rat brain membranes. This effect was not observed in membranes pretreated with EDTA. However, the effect was restored after the addition of MgCl2. The results indicate that **histogranin** blocks the access of [3H]TCP to the phencyclidine receptor located inside the NMDA-linked ion channel. Moreover, the NMDA antagonist activity of the endogenous peptide most likely requires the presence of Mg2+.

ED Entered STN: 30 Apr 1994

L33 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:208763 HCAPLUS
DOCUMENT NUMBER: 120:208763

TITLE: Phencyclidine (PCP)-like peptide, **histogranin**, modulates cell-mediated immune function
AUTHOR(S): **Lemaire, I.**; Cantin, M. F.; **Lemaire, S.**
CORPORATE SOURCE: Dep. Pharmacol., Univ. **Ottawa**, **Ottawa**, ON, Can.
SOURCE: Regulatory Peptides (1994), (Suppl. 1), S261-S262
CODEN: REPPDY; ISSN: 0167-0115
DOCUMENT TYPE: Journal
LANGUAGE: English
AB [Ser1]**histogranin** stimulated the formation of tumor necrosis factor-α (TNFα) by rat alveolar macrophages. The N-terminal fragment **histogranin**-(6-15) was as potent as the full length peptide, whereas the N-terminal fragment, **histogranin**-(1-10), and the central peptide, **histogranin**-(6-10), had no stimulatory activity.
ED Entered STN: 30 Apr 1994

L33 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:46560 HCAPLUS
DOCUMENT NUMBER: 120:46560
TITLE: Characterization of [125I][Ser1]**histogranin** binding sites in rat brain
AUTHOR(S): Rogers, Cheryl; **Lemaire, Simon**
CORPORATE SOURCE: Fac. Med., Univ. **Ottawa**, **Ottawa**, ON, Can.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 267(1), 350-6
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The binding characteristics of **histogranin** (HN), an endogenous peptide first recognized for its antagonism of N-methyl-D-aspartate (NMDA) responses, were determined in membrane prepns. of rat brain. [125I][Ser1]HN, a stable bioactive analog of HN, bound specifically and reversibly to a homogeneous population of high-affinity sites with a Kd of 25 nM and a Bmax of 410 fmol/mg protein. The binding of [125I][Ser1]HN increased linearly with membrane protein concentration and was destroyed upon membrane pretreatment with trypsin. The binding displayed rapid association and dissociation kinetics and was blocked by peptides possessing close homol. with HN in the following order: [Ser1]HN-(1-15) > HN > [Ser1]HN-(1-14) > HN-(2-15) > [Ser1]-HN-(1-10) > HN-(6-10). Unrelated peptides such as substance P, β-endorphin, neuropeptide Y, [Met5]enkephalin, [Leu5]enkephalin, dynorphin A(1-13) and neuromedin C were inactive in competition binding assays against [125I]Ser1-HN. Ligands of the binding domains of the NMDA receptor, such as (+)3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid, (+) 5-methyl-10,11-dihydro 5H-dibenzo[a, d]cyclohepten-5,10-imine hydrogen maleate, 1-N-(2-thienyl)cyclohexylpiperidine, glycine and glutamate were also ineffective in competing for [125I][Ser1]HN binding sites, interestingly, specific ligands for the polyamine site on the NMDA receptor, as well as the cations Mg++ and Zn++ inhibited [125I] [Ser1]HN binding. The polyamine antagonist diethylenetriamine produced a noncompetitive inhibition with an IC50 (175 nM) comparable to that of HN (75 nM). The cations Zn++ and Mg++ displaced [125I][Ser1]HN binding with IC50 values of 18 and 240 μM, resp. Elevated levels of [125I][Ser1]HN binding were observed in brain regions that are known to possess a high d. of NMDA receptors. The data demonstrate the presence of a [125I][Ser1]HN binding site in rat brain that may mediate the modulatory effects of the endogenous peptide on NMDA receptor functions.

ED Entered STN: 05 Feb 1994

L33 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:574728 HCAPLUS
DOCUMENT NUMBER: 119:174728
TITLE: Characterization of **histogranin** receptors in human peripheral blood lymphocytes
AUTHOR(S): **Lemaire, Simon**; Griffiths, Jenna; Lapierre, Chantal; **Lemaire, Irma**; Merali, Zulfiquar; Ravindran, Arumuga V.
CORPORATE SOURCE: Fac. Med., Univ. **Ottawa**, ON, K1H-9M5, Can.
SOURCE: Biochemical and Biophysical Research Communications (1993), 194(3), 1323-9
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Histogranin** (HN), a peptide recently isolated from bovine adrenal medulla, is also present in the spleen. In present studies, specific high affinity binding sites for HN were characterized on membrane prepns. of human lymphocytes by radioligand binding. [125I]-[Ser1]HN binding was dependent on time and protein concentration and sensitive to trypsin
treatment. The binding displayed high affinity (Kd = 1.1 nM) and saturability (Bmax = 40.2 fmol/mg protein), and it was reversed upon addition of unlabeled [Ser1]HN and closely related peptides. The relative potency of various fragments in displacing [125I]-[Ser1]HN binding indicated that the active core of the mol. resides inside the C-terminal fragment, HN-(6-15). Interestingly, depressed patients displayed a marked decrease in the binding activity (from 15.4 to 8.55 fmol/mg protein at 0.5 nM of [125I]-[Ser1]HN). The presence of high affinity HN binding sites on lymphocytes provides evidence for a modulatory role for HN in the regulation of lymphocyte functions.
ED Entered STN: 30 Oct 1993

L33 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:552249 HCAPLUS
DOCUMENT NUMBER: 119:152249
TITLE: Isolation and characterization of **histogranin**, a natural peptide with NMDA receptor antagonist activity
AUTHOR(S): **Lemaire, Simon**; Shukla, Vijay Kumar; Rogers, Cheryl; Ibrahim, Ibrahim H.; Lapierre, Chantal; Parent, Paul; Dumont, Michel
CORPORATE SOURCE: Fac. Med., Univ. **Ottawa**, **Ottawa**, ON, Can.
SOURCE: European Journal of Pharmacology, Molecular Pharmacology Section (1993), 245(3), 247-56
CODEN: EJPPET; ISSN: 0922-4106
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Histogranin**, was co-purified with bombesin-like immunoreactive peptides from bovine adrenal medulla. Its structure, H-Met-Asn-Tyr-Ala-Leu-Lys-Gly-Gln-Gly-Arg-Thr-Leu-Tyr-Gly-Phe-COOH, was determined by gas-phase Edman degradation It was in accordance with its amino acid composition and corresponded to a 15 amino acid fragment (fragment 86-100) of histone H4 with substitutions in positions 1 (Val), 2 (Val) and 7 (Arg). The peptide was synthesized by the solid-phase procedure and the synthetic product was identical to the natural peptide as determined by its retention time on three anal. high-performance liquid chromatog. systems. An antibody was raised against synthetic [Ser1]**histogranin** and used to monitor the

presence of **histogranin** in various rat tissues and subcellular fractions of bovine adrenal medulla. In rats, immunoreactive **histogranin** was mainly concentrated in the pituitary (5065 pmol/g) and the adrenal glands (268 pmol/g), but it was also present in other tissues including the brain (1.6 pmol/g) and blood plasma (24 fmol/mL). A neuropeptide function for the adrenal peptide was suggested by its relative high concentration in chromaffin granules (42 fmol/mg protein as compared with 1 fmol/mg protein in cytosol) and its release from perfused bovine adrenal glands. In rat brain membrane prepns., synthetic **histogranin** displaced the binding of [3H]CGP 39653, a specific ligand of N-methyl-D-aspartate (NMDA) receptor. The displacement curve was biphasic with IC50 of 0.6 and 3955 nM, representing 33% and 67% of the binding sites, resp. Intracerebroventricular (i.c.v.) injection of the peptide (5-100 nmol) in mice produced a dose-dependent protection against NMDA (0.5-1.0 nmol)-induced convulsions but not against (R,S)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), 0.25-2.0 nmol), kainate (0.25-0.75 nmol) and bicuculline (1-10 nmol)-induced convulsions. These results suggest that **histogranin** may be an endogenous modulator of NMDA receptor functions.

ED Entered STN: 16 Oct 1993

L33 ANSWER 18 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:291689 BIOSIS
DOCUMENT NUMBER: PREV200300291689
TITLE: **Histogranin** peptides and their analgesic use.
AUTHOR(S): **Lemaire, Simon** [Inventor, Reprint Author]
CORPORATE SOURCE: Aylmer, Canada
ASSIGNEE: University of **Ottawa**, **Ottawa**, Canada
PATENT INFORMATION: US 6566327 May 20, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (May 20 2003) Vol. 1270, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jun 2003
Last Updated on STN: 19 Jun 2003

AB The invention relates to linear and cyclic peptide and pseudopeptide compounds useful as analgesics, pharmaceutical compositions comprising such compounds, the use of the compounds and the compositions in the treatment of pain, and commercial packages containing such compounds and compositions.

ED Entered STN: 19 Jun 2003
Last Updated on STN: 19 Jun 2003

L33 ANSWER 19 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:252404 BIOSIS
DOCUMENT NUMBER: PREV200100252404
TITLE: Possible role of the dopamine D2 receptor in the analgesic effects of **Histogranin** and related peptides.
AUTHOR(S): **Lemaire, Simon** [Reprint author]; Poirier, Rene; **Le, Hoang-Thanh**; **Lemaire, Irma**; Ruan, Hong
CORPORATE SOURCE: Department of Molecular and Cellular Medicine, University of **Ottawa**, 451 Smyth Rd., **Ottawa**, Ontario, K1H-8M5, Canada
SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A226.

print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002

AB **Histogranin** (HN), a pentadecapeptide resembling to histone H4-(86-100) and osteogenic growth peptide (OGP), was assessed for its abilities to cause analgesia and modulate the specific binding of the D2 receptor ligand (3H)raclopride to rat brain membranes. HN and related fragments and analogues caused dose- and structure-dependent analgesic effects in the mouse writhing test with the following order of potency: HN-(7-15) > HN = H4-(86-100) = HN-(7-10) > (Ser1)HN (or SHN) > OGP. A high affinity saturable site for (3H)raclopride was found in rat brain membranes with a Kd of 4.87 +- 0.54 nM and a Bmax of 47.2 +- 3.01 fmol/mg protein. SHN (1 muM) produced a competitive inhibition of (3H)raclopride binding, resulting in a two fold increase in the Kd (9.35 +- 1.46 nM) but no significant change in the Bmax (44.9 +- 5.67 fmol/mg protein). In competition binding studies with 2.5 nM (3H)raclopride, SHR evoked a biphasic competition curve with a Ki for high affinity state of 32.1 +- 10.8 nM and a Ki for low affinity state of 4.43 +- 2.35 muM. Such competition profile resembled that of dopamine agonists but was distinct from those of the dopamine antagonists. The presence of NaCl (10 mM) affected the competition curve of SHN in a manner similar to that of dopamine, inducing the conversion of the high affinity state into the low affinity state with an overall Ki value of 6.54 +- 1.2 muM. The relative potencies HN and related peptides in inhibiting (3H)raclopride binding corresponded to their abilities to induce analgesia in the mouse writhing test (r = 0.86). The results indicate that HN and related peptides cause analgesia via an agonist-like interaction with the dopamine D2 receptor.
ED Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002

L33 ANSWER 20 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:108179 BIOSIS
DOCUMENT NUMBER: PREV200100108179
TITLE: Interactions of **histogranin** and related peptides with the dopamine D2 receptor in rat brain membranes.
AUTHOR(S): **Lemaire, S.** [Reprint author]; Ruan, H.
CORPORATE SOURCE: Univ **Ottawa**, **Ottawa**, ON, Canada
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-531.5. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Feb 2001
Last Updated on STN: 15 Feb 2002

AB **Histogranin** (HN) and related peptides were assessed for their ability to modulate the specific binding of the D2 receptor ligand (3H)raclopride to rat brain membranes. A high affinity saturable site for (3H)raclopride was found with a Kd of 4.87 +- 0.54 nM and a Bmax of 47.2

+- 3.01 fmol/mg protein. (Ser1)HN (1 muM), a chemically stable analogue of HN, produced a competitive inhibition of (3H)raclopride binding, resulting in a two fold increase in the Kd (9.35 +- 1.46 nM) but no significant change in the Bmax (44.9 +- 5.67 fmol/mg protein). In competition binding studies with 2.5 nM (3H)raclopride, (Ser1)HN evoked a biphasic competition curve with a Ki for high affinity state of 32.1 +- 10.8 nM and a Ki for low affinity state of 4.43 +- 2.35 muM. Such competition model was comparable to those of the dopamine agonists, dopamine and (+)3-PPP, but distinct from those of the dopamine antagonists, (-)sulpiride and (+)sulpiride (monophasic competition curves). The presence of NaCl (10 mM) affected the competition curve of (Ser1)HN in a similar manner as that of dopamine, inducing the conversion of the high affinity state into the low affinity state with an overall Ki value of 6.54 +- 1.2 muM. The relative potencies HN and related peptides in inhibiting (3H)raclopride binding are compared with their abilities to induce analgesia in the mouse writhing test. The results indicate that HN and related peptides compete with the binding of (3H)raclopride in a D2 agonist-like manner, such action of the peptides correlating well with their analgesic activity.

ED Entered STN: 28 Feb 2001
Last Updated on STN: 15 Feb 2002

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ACCESSION NUMBER: 1997:470478 BIOSIS
DOCUMENT NUMBER: PREV199799769681
TITLE: Central and peripheral non-opioid analgesic activity of **histogranin** and related peptides.
AUTHOR(S): **Lemaire, S.**; Ruan, H.; Prasad, J. A.
CORPORATE SOURCE: Dep. Pharmacol., Univ. **Ottawa**, **Ottawa**, ON K1H 8M5, Canada
SOURCE: Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 674.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1. New Orleans, Louisiana, USA. October 25-30, 1997.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Nov 1997
Last Updated on STN: 4 Nov 1997

ED Entered STN: 4 Nov 1997
Last Updated on STN: 4 Nov 1997

L33 ANSWER 22 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1997:143747 BIOSIS
DOCUMENT NUMBER: PREV199799442950
TITLE: Cytokine modulating activity of **histogranin** and related peptides.
AUTHOR(S): **Lemaire, S.**; Cantin, M. F.; **Lemaire, I.**
CORPORATE SOURCE: Dep. Pharmacol., Fac. Med., Univ. **Ottawa**, **Ottawa**, ON, Canada
SOURCE: Journal of Allergy and Clinical Immunology, (1997) Vol. 99, No. 1 PART 2, pp. S55.
Meeting Info.: Joint Meeting of the American Academy of Allergy, Asthma and Immunology, the American Association of Immunologists and the Clinical Immunology Society. San Francisco, California, USA. February 21-26, 1997.

CODEN: JACIBY. ISSN: 0091-6749.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 1997
Last Updated on STN: 2 Apr 1997
ED Entered STN: 2 Apr 1997
Last Updated on STN: 2 Apr 1997

L33 ANSWER 23 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1995:422525 BIOSIS
DOCUMENT NUMBER: PREV199598436825
TITLE: Synthesis and biological activity of **histogranin** and related peptides.
AUTHOR(S): Prasad, Jyoti; Shukla, V. K.; **Lemaire, S.**
CORPORATE SOURCE: Univ. **Ottawa**, **Ottawa**, ON K1H 8M5, Canada
SOURCE: Abstracts of Papers American Chemical Society, (1995) Vol. 210, No. 1-2, pp. MEDI 75.
Meeting Info.: 210th American Chemical Society National Meeting. Chicago, Illinois, USA. August 20-24, 1995.
CODEN: ACSRAL. ISSN: 0065-7727.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Oct 1995
Last Updated on STN: 3 Oct 1995
ED Entered STN: 3 Oct 1995
Last Updated on STN: 3 Oct 1995

L33 ANSWER 24 OF 27 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1993:345996 BIOSIS
DOCUMENT NUMBER: PREV199396042996
TITLE: Isolation and characterization of **histogranin**, a natural peptide with NMDA receptor antagonist activity.
AUTHOR(S): **Lemaire, Simon** [Reprint author]; Shukla, Vijay Kumar; Rogers, Cheryl; Ibrahim, Ibrahim H.; Lapierre, Chantal; Parent, Paul; Dumont, Michel
CORPORATE SOURCE: Dep. Pharmacol., Fac. Med., Univ. **Ottawa**, 451 Smyth Rd., **Ottawa**, Ontario, Can. K1H 8M5, canada
SOURCE: European Journal of Pharmacology Molecular Pharmacology Section, (1993) Vol. 11, No. 3, pp. 247-256.
CODEN: EJPPET. ISSN: 0922-4106.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jul 1993
Last Updated on STN: 27 Jul 1993
AB **Histogranin**, was co-purified with bombesin-like immunoreactive peptides from bovine adrenal medulla. Its structure, H-Met-Asn-Tyr-Ala-Leu-Lys-Gly-Gln-Gly-Arg-Thr-Leu-Tyr-Gly-Phe-COOH, was determined by gas-phase Edman degradation. It was in accordance with its amino acid composition and corresponded to a 15 amino acid fragment (fragment 86-100) of histone H4 with substitutions in positions 1 (Val), 2 (Val) and 7 (Arg). The peptide was synthesized by the solid-phase procedure and the synthetic product was identical to the natural peptide as determined by its retention time on three analytical high-performance liquid chromatography systems. An antibody was raised against synthetic (Ser-1) **histogranin** and used to monitor the presence of

histogranin in various rat tissues and subcellular fractions of bovine adrenal medulla. In rats, immunoreactive **histogranin** was mainly concentrated in the pituitary (50625 pmol/g) and the adrenal glands (268 pmol/g), but it was also present in other tissues including the brain (1.6 pmol/g) and blood plasma (24 fmol/ml). A neuropeptide function for the adrenal peptide was suggested by its relative high concentration in chromaffin granules (42 fmol/mg protein as compared with 1 fmol/mg protein in cytosol) and its release from perfused bovine adrenal glands. In rat brain membrane preparations, synthetic **histogranin** displaced the binding of (3H)CGP 396553, a specific ligand of N-methyl-D-aspartate (NMDA) receptor. The displacement curve was biphasic with IC-50 of 0.6 and 3955 nM, representing 33% and 67% of the binding sites, respectively. Intracerebroventricular (i.e.v.) injection of the peptide (5-100 nmol) in mice produced a dose-dependent protection against NMDA (0.5-1.0 nmol)-induced convulsions but not against (R,S)-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA, 0.25-2.0 nmol), kainate (0.25-0.75 nmol) and bicuculline (1-10 nmol)-induced convulsions. These results suggest that **histogranin** may be an endogenous modulator of NMDA receptor functions.

ED Entered STN: 26 Jul 1993
Last Updated on STN: 27 Jul 1993

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ACCESSION NUMBER: 1994-0421742 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1994 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Blockade of NMDA-induced potentiation of [.sup.3H]TCP binding to rat brain membranes by **histogranin** Towards a molecular basis in opioid research
AUTHOR: **LEMAIRE S.**; LAPIERRE C.; SHUKLA V. K.
NYBERG Fred (ed.); POST Claes (ed.); VAN REE Jan (ed.); SCHULZ Rudiger (ed.); TERENIUS Lars (ed.)
CORPORATE SOURCE: Univ. **Ottawa**, dep. pharamcology, **Ottawa** ON K1H 8M5, Canada
Uppsala univ., dep. pharmaceutical biosci., 75185 Uppsala, Sweden
SOURCE: Regulatory peptides, (1994) (SUP1), S271-S272, 5 refs.
Conference: 24 INRC : international narcotics research conference, Skoevde (Sweden), 10 Jul 1993
ISSN: 0167-0115 CODEN: REPPDY
DOCUMENT TYPE: Journal; Conference
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Netherlands
LANGUAGE: English
AVAILABILITY: INIST-18854, 354000049337691340

AN 1994-0421742 PASCAL
CP Copyright .COPYRGT. 1994 INIST-CNRS. All rights reserved.
AB **Histogranin** (H-Met-Asn-Tyr-Ala-Leu-Lys-Gly-Gln-Gly-ArB-Thr-Leu-Tyr-Gly-Phe-COOH) was first isolated from bovine adrenal medulla (1) and shown to antagonize 'in vitro' N-methyl-D-aspartate (NMDA)-induced locus coeruleus cell depolarization (unpublished) and 'in vivo' NMDA-induced mouse convulsions. **Histogranin** possesses its own high affinity saturable binding site in rat brain membranes insensitive to the presence of NMDA (2). On the other hand, **histogranin** is a potent non-competitive inhibitor of the binding of the NMDA receptor ligand, [.sup.3H]CGP 39653 (1)
UP 20001027

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on STN
ACCESSION NUMBER: 1994-0421737 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1994 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Phencyclidine (PCP)-like peptide, **histogranin**, modulates cell-mediated immune function
Towards a molecular basis in opioid research
AUTHOR: **LEMAIRE I.**; CANTIN M.-F.; **LEMAIRE S.**
NYBERG Fred (ed.); POST Claes (ed.); VAN REE Jan (ed.); SCHULZ Rudiger (ed.); TERENIUS Lars (ed.)
CORPORATE SOURCE: Univ. **Ottawa**, dep. pharmacology, **Ottawa** ON, Canada
Uppsala univ., dep. pharmaceutical biosci., 75185 Uppsala, Sweden
SOURCE: Regulatory peptides, (1994) (SUP1), S261-S262, 9 refs.
Conference: 24 INRC : international narcotics research conference, Skoevde (Sweden), 10 Jul 1993
ISSN: 0167-0115 CODEN: REPPDY
DOCUMENT TYPE: Journal; Conference
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Netherlands
LANGUAGE: English
AVAILABILITY: INIST-18854, 354000049337691290
AN 1994-0421737 PASCAL
CP Copyright .COPYRGT. 1994 INIST-CNRS. All rights reserved.
AB **Histogranin**, a peptide originally isolated from the adrenal medulla was shown to exhibit PCP-like activities including significant blockade of NMDA-induced convulsions in mice (1), and induction of locomotion, ataxia and stereotypy in rats (submitted). Besides its localization in the brain and adrenal medulla, HN was found to be present in significant levels in the lung and spleen (submitted). In previous studies, we have shown that both macrophages and lymphocytes are targets for HN action (submitted) and we have demonstrated that HN stimulates the production of interleukin-1 (IL-1) and interleukin-6 (IL-6), two cytokines known to play a prominent role in immunoregulation (2)
UP 20001027

L33 ANSWER 27 OF 27 DRUGU COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-35930 DRUGU P
TITLE: Possible role of the dopamine D2 receptor in the analgesic effects of **histogranin** and related peptides.
AUTHOR: **Lemaire S**; Poirier R; **Le H T**; **Lemaire I**; Ruan H
CORPORATE SOURCE: Univ.**Ottawa**
LOCATION: Ottawa, Ont., Can.
SOURCE: FASEB J. (15, No. 4, A226; 2001)
CODEN: FAJOEC ISSN: 0892-6638
AVAIL. OF DOC.: Department of Molecular and Cellular Medicine, University of **Ottawa**, 451 Smyth Rd., **Ottawa**, Ontario K1H 8M5, Canada.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2001-35930 DRUGU P
AB The analgesic activity of **histogranin** (HN) and related peptides, including (Ser)HN, osteogenic growth peptide and histone H4-86-100 was studied in mice. Relative analgesic potency was correlated with dopamine D2 receptor binding in rat brain membranes in-vitro. It is concluded that the analgesic activity of HN-like peptides is mediated by

D2 agonist activity. (conference abstract: Experimental Biology 2001, Orlando, Florida, USA).

ABEX HN and structurally related peptides inhibited writhing in mice in the decreasing order of potency HN-7-15: HN: histone H4-86-100: HN-7-10: (Ser)HN: osteogenic growth peptide. (Ser)HN 1 uM inhibited 3H-raclopride binding to rat brain membranes in a competitive manner, increasing the Kd from 4.87 to 9.35 nM without affecting Bmax. In the presence of 3H-raclopride 2.5 nM, (Ser)HN showed a biphasic competition curve with high and low affinity Ki of 32.1 nM and 4.43 uM respectively. NaCl 10 mM had similar effects on the competition curves of (Ser)HN and dopamine, converting the high affinity state to a low affinity state with a Ki of 6.54 uM. The relative potencies of HN and related peptides in the writhing test corresponded to their receptor binding profiles. (E33/JB)

=>
=>

=> fil lreg

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STRUCTURE FILE UPDATES: 19 DEC 2004 HIGHEST RN 799762-98-4
DICTIONARY FILE UPDATES: 19 DEC 2004 HIGHEST RN 799762-98-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
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Experimental and calculated property data are now available. For more
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http://www.cas.org/ONLINE/DBSS/registryss.html

=> fil hcap

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FILE COVERS 1907 - 21 Dec 2004 VOL 141 ISS 26
FILE LAST UPDATED: 20 Dec 2004 (20041220/ED)

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=> fil uspatfull

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 21 Dec 2004 (20041221/PD)
FILE LAST UPDATED: 21 Dec 2004 (20041221/ED)
HIGHEST GRANTED PATENT NUMBER: US6834393
HIGHEST APPLICATION PUBLICATION NUMBER: US2004255355
CA INDEXING IS CURRENT THROUGH 21 Dec 2004 (20041221/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 21 Dec 2004 (20041221/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2004

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

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>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
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>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
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FILE CONTENT:1840 - 19 Dec 2004 VOL 141 ISS 25

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=> fil toxcenter

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TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

=> fil medlin

FILE 'MEDLINE' ENTERED AT 09:53:24 ON 21 DEC 2004

FILE LAST UPDATED: 20 DEC 2004 (20041220/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil biosis

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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 16 December 2004 (20041216/ED)

FILE RELOADED: 19 October 2003.

=> fil embase

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FILE COVERS 1974 TO 17 Dec 2004 (20041217/ED)

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=> fil wpix

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FILE LAST UPDATED: 16 DEC 2004 <20041216/UP>
MOST RECENT DERWENT UPDATE: 200481 <200481/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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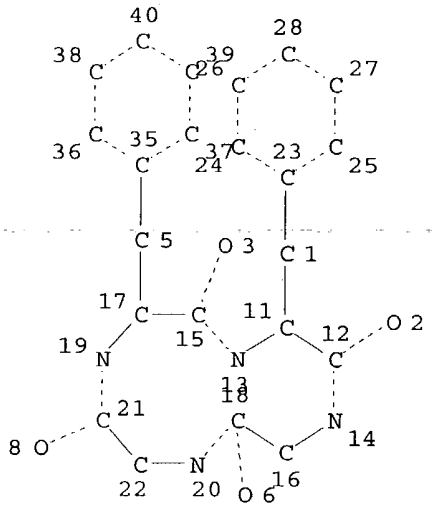
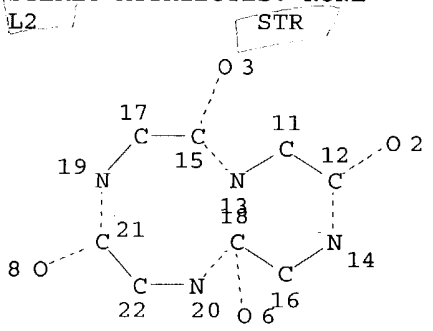
=> d que l4
L1 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 30

STEREO ATTRIBUTES: NONE
L2 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L3 (125) SEA FILE=REGISTRY SSS FUL L2
L4 8 SEA FILE=REGISTRY SUB=L3 SSS FUL L1

=> d que nos 15
L1 STR
L2 STR
L3 (125) SEA FILE=REGISTRY SSS FUL L2

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L4              8 SEA FILE=REGISTRY SUB=L3 SSS FUL L1
L5             10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4


=> d que nos l6
L1                STR
L2                STR
L3   (       125)SEA FILE=REGISTRY SSS FUL L2
L4              8 SEA FILE=REGISTRY SUB=L3 SSS FUL L1
L6              1 SEA FILE=USPATFULL ABB=ON  PLU=ON  L4


=> d que nos l7
L1                STR
L2                STR
L3   (       125)SEA FILE=REGISTRY SSS FUL L2
L4              8 SEA FILE=REGISTRY SUB=L3 SSS FUL L1
L7              1 SEA FILE=CASREACT ABB=ON  PLU=ON  L4


=> d que nos l8
L1                STR
L2                STR
L3   (       125)SEA FILE=REGISTRY SSS FUL L2
L4              8 SEA FILE=REGISTRY SUB=L3 SSS FUL L1
L8              1 SEA FILE=TOXCENTER ABB=ON  PLU=ON  L4


=>

     (FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 09:08:10 ON 21 DEC 2004)

=>

=> d que nos l11
L1                STR
L2                STR
L3   (       125)SEA FILE=REGISTRY SSS FUL L2
L4              8 SEA FILE=REGISTRY SUB=L3 SSS FUL L1
L9                SEL  PLU=ON  L4  1-  CHEM :       23 TERMS
L10             3 SEA L9
L11             2 DUP REM L10 (1 DUPLICATE REMOVED)


=> d que l19
L12           370 SEA FILE=WPIX ABB=ON  PLU=ON  C07K005-12/IPC
L13         41498 SEA FILE=WPIX ABB=ON  PLU=ON  A61K038?/IPC
L14           229 SEA FILE=WPIX ABB=ON  PLU=ON  L12 AND L13
L15          5930 SEA FILE=WPIX ABB=ON  PLU=ON  (C07C279? OR C07D235?)/IPC
L16             3 SEA FILE=WPIX ABB=ON  PLU=ON  L14 AND L15
L17             1 SEA FILE=WPIX ABB=ON  PLU=ON  US6566327/PN
L18             1 SEA FILE=WPIX ABB=ON  PLU=ON  L16 AND L17
L19             3 SEA FILE=WPIX ABB=ON  PLU=ON  L16 OR L18


=> dup rem l5 l6 l7 l8 l11 l19

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PROCESSING COMPLETED FOR L8
PROCESSING COMPLETED FOR L11
PROCESSING COMPLETED FOR L19
L34 14 DUP REM L5 L6 L7 L8 L11 L19 (4 DUPLICATES REMOVED)
ANSWERS '1-10' FROM FILE HCAPLUS
ANSWER '11' FROM FILE USPATFULL
ANSWER '12' FROM FILE EMBASE
ANSWERS '13-14' FROM FILE WPIX

=> FIL STNGUIDE

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=> d ibib abs ed hitstr
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(Y)/N:y

L34 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:633749 HCAPLUS
DOCUMENT NUMBER: 139:180347
TITLE: Preparation of histogranin-like peptides and non-peptides
INVENTOR(S): Lemaire, Simon; Bernatchez-Lemaire, Irma; Le, Hoang-Tanh
PATENT ASSIGNEE(S): University of Ottawa, Can.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003066673	A1	20030814	WO 2003-CA148	20030205
WO 2003066673	C1	20031204		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003176329	A1	20030918	US 2002-68905	20020207
EP 1481002	A1	20041201	EP 2003-737222	20030205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			US 2002-68905	A 20020207
			WO 2003-CA148	W 20030205

OTHER SOURCE(S): MARPAT 139:180347
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to new basic amino acid derivs. I, II and III [A is H, alkyl, or hydroxyalkyl; B is guanidinoalkyl, 4-imidazolylalkyl, aminoalkyl, p-aminophenylalkyl, p-guanidinophenylalkyl, or 4-pyridinylalkyl; D is CO, CO-alkylene, or alkylene; E is a single bond or alkylene; Z is NH2, amino groups, OH, alkoxy, benzyloxy, or halobenzyl; R1-R5 are independently H or various substituents] and to their preparation and use in treatment of pain. The compds. have histogranin-like antinociceptive, morphine potentiating and COX-2 induction modulating activities. Thus, cyclo[Gly-(p-chloro)Phe-Tyr-D-Arg] (I-1) was prepared on an oxime resin using tert-butoxycarbonyl (Boc) protection and cleaved from the resin using intrachain aminolysis in the presence of AcOH and diisopropylethylamine. I-1 showed AD50 = 0.17 nmol/mouse and an analgesic potency ratio of 135 relative to histogranin in a mouse writhing pain assay.

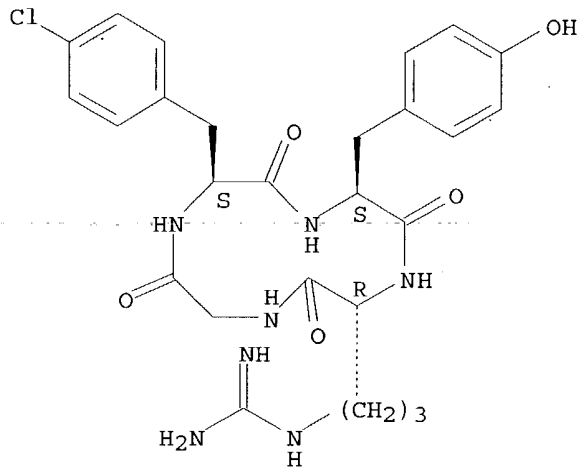
ED Entered STN: 15 Aug 2003

IT **565468-97-5P 565468-98-6P 573720-47-5P 573720-48-6P 573720-49-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of histogranin-like peptides and non-peptides)

RN 565468-97-5 HCAPLUS

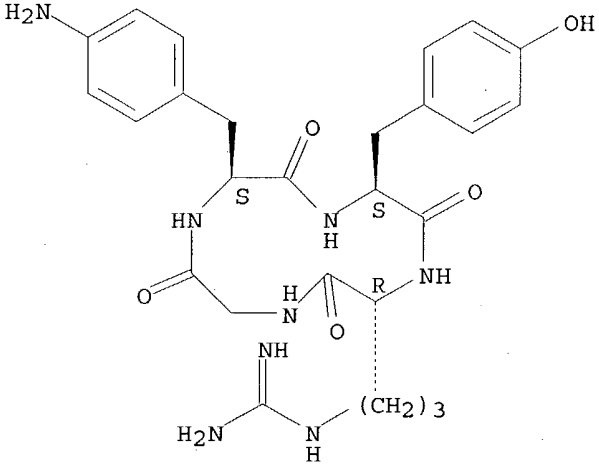
CN Cyclo(D-arginylglycyl-4-chloro-L-phenylalanyl-L-tyrosyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



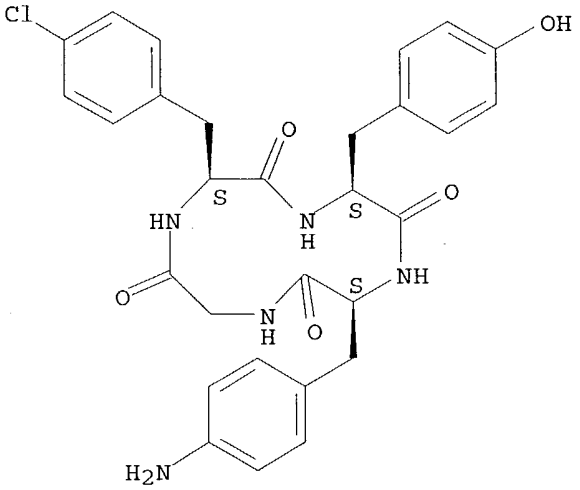
RN 565468-98-6 HCAPLUS
CN Cyclo(D-arginylglycyl-4-amino-L-phenylalanyl-L-tyrosyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



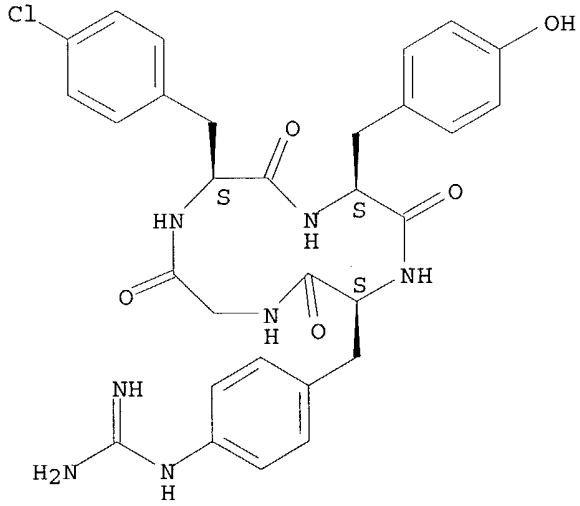
RN 573720-47-5 HCAPLUS
CN Cyclo(glycyl-4-chloro-L-phenylalanyl-L-tyrosyl-4-amino-L-phenylalanyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



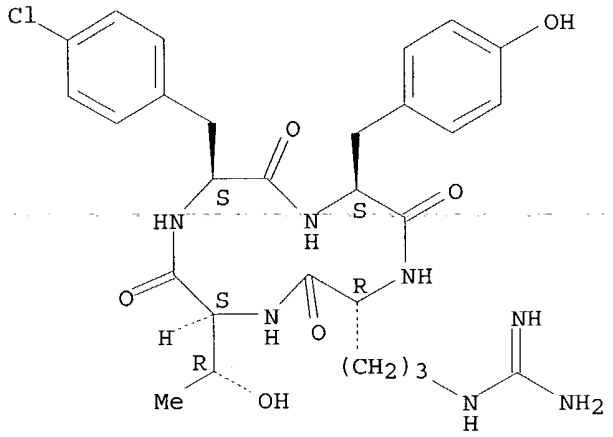
RN 573720-48-6 HCAPLUS
CN Cyclo[glycyl-4-chloro-L-phenylalanyl-L-tyrosyl-4-[(aminoiminomethyl)amino]-L-phenylalanyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 573720-49-7 HCAPLUS
CN Cyclo(D-arginyl-L-threonyl-4-chloro-L-phenylalanyl-L-tyrosyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs ed hitstr 2-10
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, EMBASE, WPIX' - CONTINUE? (Y)/N:y

L34 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:421338 HCAPLUS
DOCUMENT NUMBER: 139:133827
TITLE: Bioactive Peptidic Analogues and Cyclostereoisomers of the Minimal Antinociceptive Histogranin Fragment-(7-10)
AUTHOR(S): Le, Hoang-Thanh; Lemaire, Irma B.; Gilbert, Annie-Kim; Jolicoeur, Francois; Lemaire, Simon
CORPORATE SOURCE: Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, K1H 8M5, Can.
SOURCE: Journal of Medicinal Chemistry (2003), 46(14), 3094-3101
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:133827
AB Novel analogs of the minimal antinociceptive histogranin (HN) fragment Gly7-Gln8-Gly9-Arg10, in which amino acids in positions 8-10 were replaced by lipophilic amino acids and corresponding D-amino acid residues in combination with N- to C-terminal cyclization, were synthesized and tested in various animal models of pain. All synthetic peptides were potent and efficacious analgesics in the mouse writhing test. Cyclo[Gly-Ala-Tyr-D-Arg] (9) and cyclo[Gly-p-Cl-Phe-Tyr-D-Arg] (10) were the most potent analgesics, being 17 and 135 times as potent as HN, resp. (AD50 of 1.37 and 0.17 nmol/mouse icv, as compared with 23 nmol/mouse for HN). The times of action of compds. 9 and 10 were also much improved with half-maximal effects still being observed 60 min and >90 min after their administration, resp., as compared with 8.1 min for the parent peptide HN-(7-10) and 22.1 min for HN. At analgesic doses, compds. 9 and 10 were

devoid of motor effect as assessed by the mouse rotarod assay. As already observed with HN, compds. 9 (10 nmol/rat; i.t.) and 10 (0.5 nmol/rat; i.t.) were effective in blocking persistent inflammatory pain in the formalin test and hyperalgesia induced by intraplantar administration of complete Freund adjuvant. In addition, the analgesic effects evoked by compds. 9 (10 nmol/mouse; icv) and 10 (1 μmol/kg; i.v.) in the mouse writhing test and compound 9 (10 nmol/mouse; icv) in the mouse tail flick assay were similarly antagonized by the dopamine D2 receptor antagonist raclopride (1 nmol/mouse; icv) but not the opiate antagonist naloxone (1 nmol/mouse; icv). Finally, the various cyclic peptides competed with the binding of [3H]raclopride in rat brain membrane prepns. Their ability to compete with the binding of the D2 ligand correlated well with their potency in alleviating pain in the mouse writhing test (r = 0.95). These results indicate that the analgesic activity of the minimal active core in HN can be improved by changes that favor its interaction with the dopamine D2 receptor.

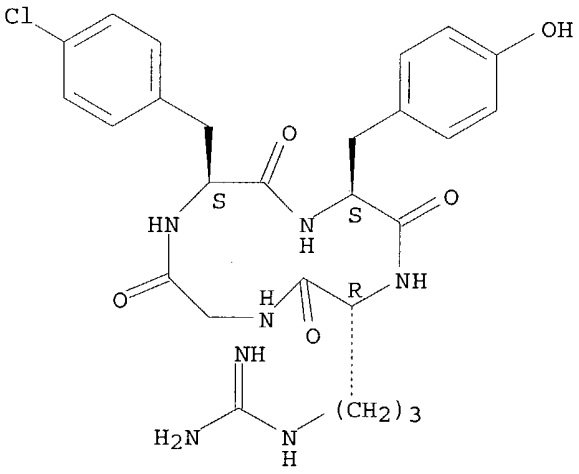
ED Entered STN: 03 Jun 2003

IT **565468-97-5P 565468-98-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and analgesic activity of cyclic peptide analogs of histogranin(7-10))

RN 565468-97-5 HCAPLUS

CN Cyclo(D-arginylglycyl-4-chloro-L-phenylalanyl-L-tyrosyl) (9CI) (CA INDEX NAME)

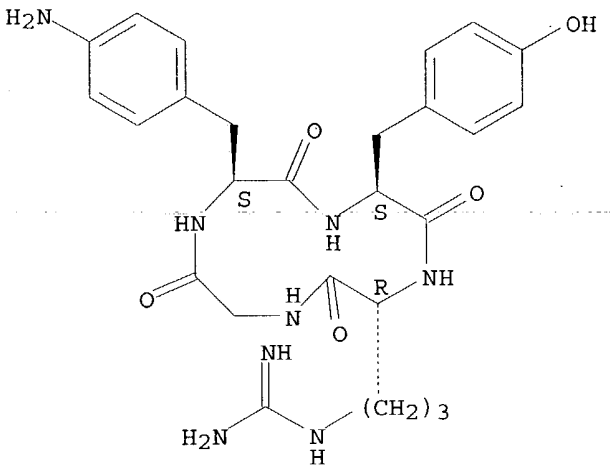
Absolute stereochemistry.



RN 565468-98-6 HCAPLUS

CN Cyclo(D-arginylglycyl-4-amino-L-phenylalanyl-L-tyrosyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



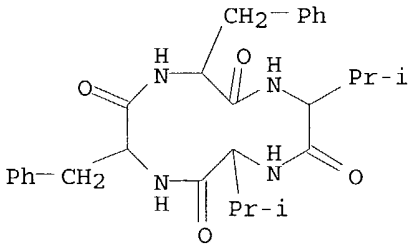
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2000:772490 HCAPLUS
DOCUMENT NUMBER: 133:340213
TITLE: Antibody conjugates for delivery of antimicrobial toxins
INVENTOR(S): Carlyle, Wenda C.
PATENT ASSIGNEE(S): St. Jude Medical, Inc., USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

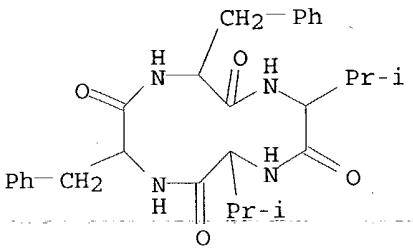
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064487	A2	20001102	WO 2000-US8389	20000330
W: BR, JP, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1212094	A2	20020612	EP 2000-921508	20000330
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
BR 2000009947	A	20021231	BR 2000-9947	20000330
JP 2003523315	T2	20030805	JP 2000-613477	20000330
ZA 2001008639	A	20030730	ZA 2001-8639	20011019
PRIORITY APPLN. INFO.:			US 1999-298638 A	19990423
			WO 2000-US8389 W	20000330

AB An antimicrobial conjugate (100, 120, 154) can be formed that includes an antibody (100, 122) or ligand bonded to an antimicrobial agent (106, 124). The antibody (102, 122, 154) or ligand has an affinity for microbial antigens or receptors. The antimicrobial conjugate (100, 120, 154) can be used alone or associated with biocompatible material (152) incorporated into a medical device (150). An antimicrobial conjugate (100, 120, 154) can be placed in contact with a solution to eliminate viable microorganisms from the solution In particular, the antimicrobial conjugate (100, 120, 154) can be used to reduce the risk of infection associated with the contact of a medical

device with patient's bodily fluids or tissues.
ED Entered STN: 03 Nov 2000
IT **24181-12-2D**, Fungisporin, antibody conjugates
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antibody conjugates for delivery of antimicrobial toxins)
RN 24181-12-2 HCAPLUS
CN Cyclo(D-phenylalanyl-L-phenylalanyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)



L34 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 1969:524896 HCAPLUS
DOCUMENT NUMBER: 71:124896
TITLE: Synthesis and structure of fungisporin
AUTHOR(S): Studer, Rolf O.
CORPORATE SOURCE: Chem. Res. Dep., F. Hoffmann-La Roche and Co. A.-G., Basel, Switz.
SOURCE: Experientia (1969), 25(9), 899
CODEN: EXPEAM; ISSN: 0014-4754
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fungisporin, a cyclooctapeptide, was previously reported as having the structure cyclo-(Phe-Val)4. Sequence studies indicated cyclo-(D-Val-L-Val-D-Phe-L-Phe)2. Z-L-Phe-D-Val-L-Val-D-Phe-O-Bu-tert (I) was prepared by the stepwise elongation using the N-hydroxysuccinimide esters of the corresponding Z-amino acids. When I was treated with F3CCO2H, the tert-BuO group was removed and the resulting Z-tetrapeptide was activated with bis(p-nitrophenyl) sulfite and the Z group removed with HBr-AcOH. The p-nitrophenyl ester was cyclized under high dilution in pyridine to give a product with mol. weight 482 by mass spectrometry which indicated a cyclic tetrapeptide. Natural fungisporin also has mol. weight 482. (Z-PhCH2O2C)
ED Entered STN: 12 May 1984
IT **24181-12-2**
RL: PRP (Properties)
(structure of)
RN 24181-12-2 HCAPLUS
CN Cyclo(D-phenylalanyl-L-phenylalanyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)



L34 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1980:406071 HCAPLUS
DOCUMENT NUMBER: 93:6071
TITLE: Gushing-inducing peptides in beer produced by Penicillium chrysogenum
AUTHOR(S): Kitabatake, Katsuaki; Fukushima, Shuji; Kawasaki, Ichiro; Amaha, Mikio
CORPORATE SOURCE: Cent. Res. Lab., Asahi Brew. Ltd., Tokyo, 143, Japan
SOURCE: Peptide Chemistry (1980), Volume Date 1979, 17th, 7-12
CODEN: PECHDP; ISSN: 0388-3698
DOCUMENT TYPE: Journal
LANGUAGE: English

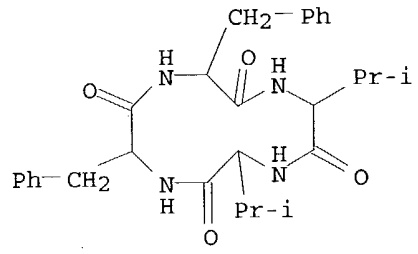
AB A cyclic peptide that induced gushing in bottled beer was isolated from culture filtrates of P. chrysogenum. It was identified as cyclo-D-Val-L-Val-D-Phe-L-Phe (I) [**24181-12-2**]. Another factor inducing beer gushing was isolated that was a mixture of I and other tetrapeptides containing valine, phenylalanine, and tyrosine. The gushing caused by several natural and synthetic peptides was examined and the results are tabulated. Cyclic structure was important; little or no gushing was induced by linear peptides.

ED Entered STN: 12 May 1984

IT **24181-12-2**
RL: BIOL (Biological study)
(beer gushing caused by, from Penicillium chrysogenum)

RN 24181-12-2 HCAPLUS

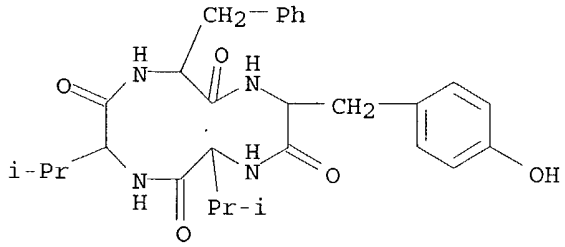
CN Cyclo(D-phenylalanyl-L-phenylalanyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)



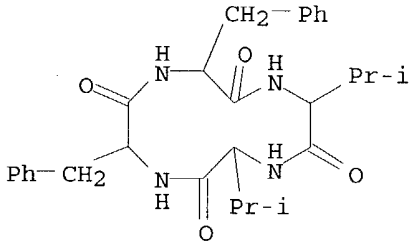
IT **73787-51-6 73804-19-0**
RL: BIOL (Biological study)
(beer gushing induction by)

RN 73787-51-6 HCAPLUS

CN Cyclo(D-phenylalanyl-L-tyrosyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)

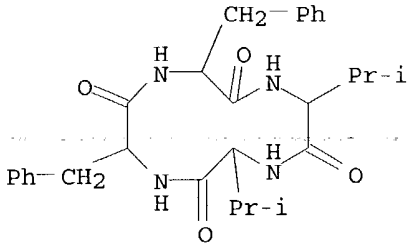


RN 73804-19-0 HCAPLUS
CN Cyclo(L-phenylalanyl-D-phenylalanyl-L-valyl-D-valyl) (9CI) (CA INDEX NAME)

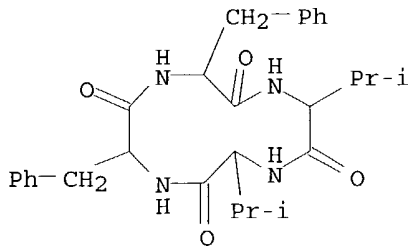


L34 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1978:23373 HCAPLUS
DOCUMENT NUMBER: 88:23373
TITLE: Synthesis of biologically active cyclic peptides and depsipeptides by the phosphite method
AUTHOR(S): Rothe, M.; Kreiss, W.
CORPORATE SOURCE: Org.-Chem. Inst., Univ. Mainz, Mainz, Fed. Rep. Ger.
SOURCE: Pept., Proc. Eur. Pept. Symp., 14th (1976), 71-8. Editor(s): Loffet, Albert. Editions Univ. Bruxelles: Brussels, Belg.
CODEN: 36PZAV
DOCUMENT TYPE: Conference
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB H-(Val-D-Hyv-D-Val-L-Lac)n-OH [I; Hyv = OCH(CHMe2)CO, Lac = OCHMeCO, n = 3] was cyclized by the phosphite method in toluene or diethyl phosphite (DEP) to give cyclo(Val-D-Hyv-D-Val-L-Lac)m (II; m = 3) (valinomycin) in 24 or 56% yields, whereas I (n = 1, 2) were cyclized by the phosphite method in toluene or DEP to give II (m = 1-4, 6). II (m = 1) had a very stable crystal lattice and its IR spectrum gave no indication of cis peptide bonds. Antamanide (III) was prepared by the phosphite-mediated cyclization of H-Phe-Phe-Val-Pro-Pro-Ala-Phe-Phe-Pro-Pro-OH (IV) or H-Pro-Ala-Phe-Phe-Pro-Pro-Phe-Phe-Val-Pro (V); IV always gave higher yields than V. Protected gramicidin S cyclo[Val-Orn(Pht)-Leu-D-Phe-Pro]p (VI, Pht = phthalyl, p = 2], protected semigramicidin S VI (p = 1), and cyclo(D-Phe-Phe-D-Val-Val) (fungisporin) were also prepared by the phosphite method.
ED Entered STN: 12 May 1984
IT **24181-12-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, by phosphite method)
RN 24181-12-2 HCAPLUS

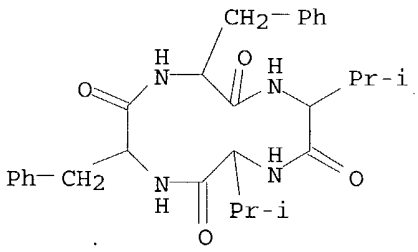
CN Cyclo(D-phenylalanyl-L-phenylalanyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)



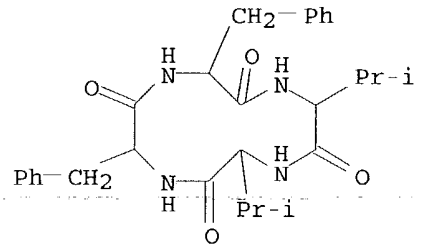
L34 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1961:20839 HCAPLUS
DOCUMENT NUMBER: 55:20839
ORIGINAL REFERENCE NO.: 55:4102g-i
TITLE: Monolayers of some cyclic peptides. Fungisporin and gramicidin J1
AUTHOR(S): Ikeda, Shoichi; Isemura, Toshizo
CORPORATE SOURCE: Univ. Osaka
SOURCE: Bulletin of the Chemical Society of Japan (1960), 33, 753-60
CODEN: BCSJA8; ISSN: 0009-2673
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Surface pressure, potential, and viscosity of monolayers at the air-water interface were studied. Fungisporin (I) and gramicidin J1 (II) assumed configurations permitting the maximum number of 7-membered H-bonded rings, 4 and
3, resp. I may then have 4 equally probable configurations and II may have 2 of unequal probability, with side chains of D- and L-amino acids oriented in opposite directions. I formed condensed monolayers. Un-ionized II at pH 11.2 gave more expanded monolayers ascribed to the presence of a prolyl rather than the ornithyl moieties. The behavior of ionized II over a neutral phase containing KCl agreed with properties predicted when involvement of but one ornithyl moiety in forming the elec. double layer was assumed. The other ornithyl side chain was probably oriented outward.
ED Entered STN: 22 Apr 2001
IT **24181-12-2**, Fungisporin
(films (unimol.) of)
RN 24181-12-2 HCAPLUS
CN Cyclo(D-phenylalanyl-L-phenylalanyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)



L34 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1960:97263 HCAPLUS
DOCUMENT NUMBER: 54:97263
ORIGINAL REFERENCE NO.: 54:18379g-h
TITLE: Fungisporin. III. The structure of fungisporin
AUTHOR(S): Miyao, Kohei
CORPORATE SOURCE: Univ. Tokyo
SOURCE: Bulletin of the Agricultural Chemical Society of Japan (1960), 24, 23-30
CODEN: BACOAV; ISSN: 0375-8397
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. CA 50, 16962b. The most probable structure of fungisporin was presented as cyclodi(D-valyl-L-valyl-D-phenylalanyl-L-phenylalanine).
ED Entered STN: 22 Apr 2001
IT **24181-12-2**, Fungisporin
(structure of)
RN 24181-12-2 HCAPLUS
CN Cyclo(D-phenylalanyl-L-phenylalanyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)



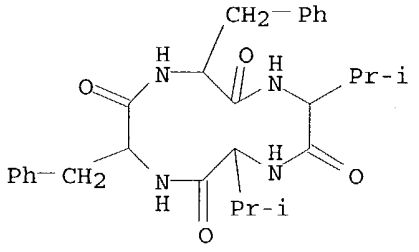
L34 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1956:90024 HCAPLUS
DOCUMENT NUMBER: 50:90024
ORIGINAL REFERENCE NO.: 50:16962b-c
TITLE: Fungisporin. II
AUTHOR(S): Miyao, Kohei
CORPORATE SOURCE: Univ. Tokyo
SOURCE: Bulletin of the Agricultural Chemical Society of Japan (1955), 19, 86-91
CODEN: BACOAV; ISSN: 0375-8397
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C.A. 47, 9406i. The exptl. formula in the previous paper for fungisporin (I) should be corrected to (C14H18N2O2)x. I was subjected to acid and alkali hydrolysis and L-phenylalanine and L-valine were identified in the hydrolyzate. From the results of the determination of each amino acid and infrared spectrum, I was found to be a polypeptide composed of equimol. amts. of the 2 amino acids.
ED Entered STN: 22 Apr 2001
IT **24181-12-2**, Fungisporin
(preparation of)
RN 24181-12-2 HCAPLUS
CN Cyclo(D-phenylalanyl-L-phenylalanyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)



L34 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1953:55348 HCAPLUS
DOCUMENT NUMBER: 47:55348
ORIGINAL REFERENCE NO.: 47:9406i,9407a-b
TITLE: Fungisporin. I
AUTHOR(S): Sumiki, Yusuke; Miyao, Kohei
CORPORATE SOURCE: Univ. Tokyo
SOURCE: Nippon Nogei Kagaku Kaishi (1952), 26, 27-31
CODEN: NNKKAA; ISSN: 0002-1407
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB A new compound was obtained as the crystalline sublimate by destructive distillation of several species of Penicillium and Aspergillus. It is one of the components of the spores and not a product formed by destructive distillation This substance, fungisporin (I), has the empirical formula, (C13H16O2N2)x, m. 355-60° (decomposition) in a sealed tube. Under atmospheric pressure and reduced pressure I sublimed at 280°. I was not soluble in most organic and inorg. solvents. Therefore, its alkyl and acyl derivs. could not be prepared I with concentrated HNO3 gave p-nitrobenzoic acid and a crystalline, N-containing substance, m. 132-5°. I with concentrated HCl gave a primary amine with exptl. formula C8H13O2N. The infrared absorption spectrum showed the existence of CH:CH, CONH2, CH2, and Me, and either OH or NH. Thus I was presumed to be a high-mol. substance somewhat similar to a simple protein.

ED Entered STN: 22 Apr 2001
IT **24181-12-2**, Fungisporin
(preparation of)
RN 24181-12-2 HCAPLUS
CN Cyclo(D-phenylalanyl-L-phenylalanyl-D-valyl-L-valyl) (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 11
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, EMBASE, WPIX' - CONTINUE?
(Y)/N:y

L34 ANSWER 11 OF 14 USPATFULL on STN
ACCESSION NUMBER: 2003:251540 USPATFULL
TITLE: Histogranin-like peptides and non-peptides, processes for their preparation and uses thereof
INVENTOR(S): Lemaire, Simon, Quebec, CANADA
Bernatchez-Lemaire, Irma, Quebec, CANADA
Le, Hoang-Thanh, Ottawa, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003176329	A1	20030918
APPLICATION INFO.:	US 2002-68905	A1	20020207 (10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Gerald T. Shekleton, Esq., Welsh & Katz, Ltd., 22nd Floor, 120 S. Riverside Plaza, Chicago, IL, 60606
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 1085
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to new basic amino acid derivatives of general formulae I, II and III, and the preparation and use thereof in treatment of pain. The compounds have histogranin-like antinociceptive, morphine potentiating and COX-2 induction modulating activities. ##STR1##

wherein:

A is -hydrogen, --(C.sub.1-C.sub.8)alkyl or --(C.sub.1-C.sub.8)alkyl substituted by hydroxy;

B is --(C.sub.1-C.sub.6)alkylguanidino, --(C.sub.1-C.sub.6)alkyl(4-imidazolyl), --(C.sub.1-C.sub.6)alkylamino, p-aminophenylalkyl(C.sub.1-C.sub.6)--, p-guanidinophenylalkyl(C.sub.1-C.sub.6)-- or 4-pyridinylalkyl(C.sub.1-C.sub.6)--;

D is --(CO)--, --(CO)--(C.sub.1-C.sub.6)alkylene or --(C.sub.1-C.sub.6)alkylene;

E is a single bond or --(C.sub.1-C.sub.6)alkylene;

Z is --NH.sub.2, --NH--(C.sub.1-C.sub.6)alkylcarboxamide, --NH--(C.sub.1-C.sub.6)alkyl, --NH--(N-benzyl), --NH-cyclo(C.sub.5-C.sub.7)alkyl, --NH-2-(1-piperidyl)ethyl, --NH-2-(1-pyrrolidyl)ethyl, --NH-2-(1-pyridyl)ethyl, --NH-2-(morpholino)ethyl, -morpholino, -piperidyl, --OH, --(C.sub.1-C.sub.6)alkoxy, --O-benzyl or --O-halobenzyl;

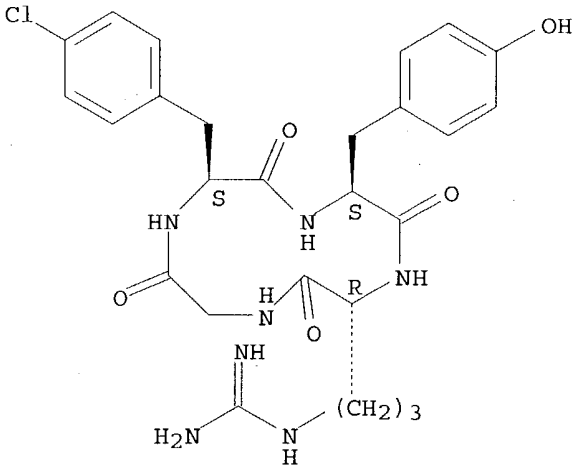
R.sup.1, R.sup.2 and R.sup.3 are, independent of one another, -hydrogen, -arylcarbonylamino, --(C.sub.1-C.sub.6)alkoylamino, --(C.sub.1-C.sub.6)alkylamino, --(C.sub.1-C.sub.6)alkyloxy, --(C.sub.1-C.sub.6)alkylaminocarbonyl, -carboxy, --OH, -benzoyl, -p-halogenobenzoyl, -methyl, --S-(2,4-dinitrophenyl), --S-(3-nitro-2-pyridinesulfenyl), -sulfonyl, -trifluoromethyl,

--(C.sub.1-C.sub.6)alkylaminocarbonylamino, -halo or -amino;

R.sup.4 and R.sup.5 are, independent of one another, -hydrogen, --(C.sub.1-C.sub.6)alkyl, -methyloxy, -nitro, -amino, -arylcarbonylamino, --(C.sub.1-C.sub.6)alkoylamino, --(C.sub.1-C.sub.6)alkylamino, -halo or --OH.

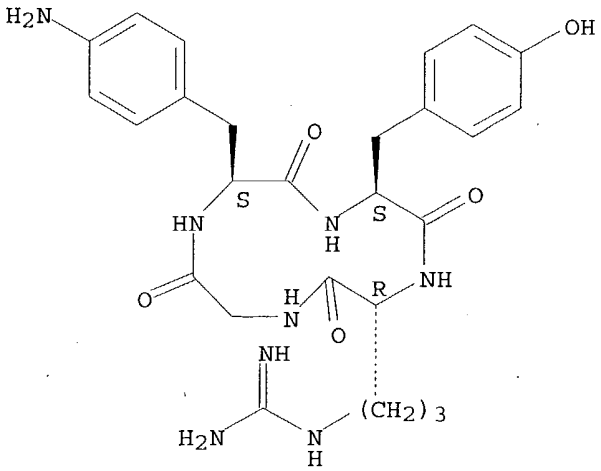
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **565468-97-5P 565468-98-6P 573720-47-5P**
573720-48-6P 573720-49-7P
(preparation of histogranin-like peptides and non-peptides)
RN 565468-97-5 USPATFULL
CN Cyclo(D-arginylglycyl-4-chloro-L-phenylalanyl-L-tyrosyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



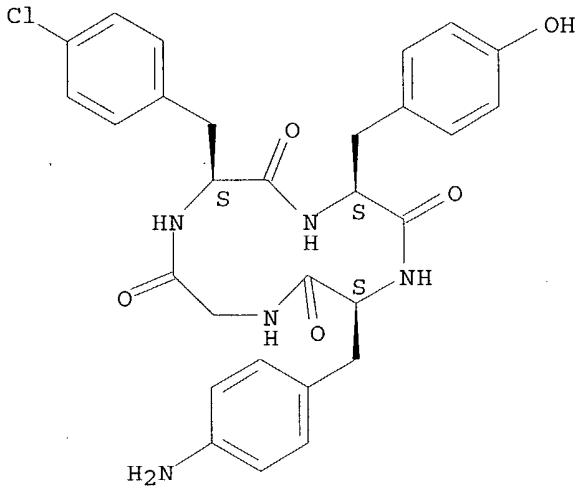
RN 565468-98-6 USPATFULL
CN Cyclo(D-arginylglycyl-4-amino-L-phenylalanyl-L-tyrosyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



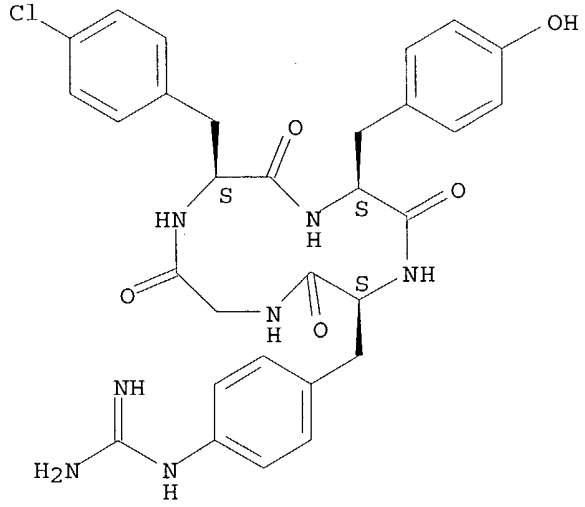
RN 573720-47-5 USPATFULL
CN Cyclo(glycyl-4-chloro-L-phenylalanyl-L-tyrosyl-4-amino-L-phenylalanyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



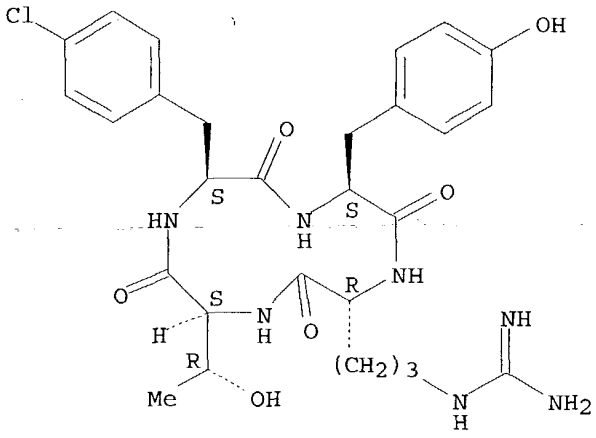
RN 573720-48-6 USPATFULL
CN Cyclo[glycyl-4-chloro-L-phenylalanyl-L-tyrosyl-4-[(aminoiminomethyl)amino]-L-phenylalanyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 573720-49-7 USPATFULL
CN Cyclo(D-arginyl-L-threonyl-4-chloro-L-phenylalanyl-L-tyrosyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs 12
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, EMBASE, WPIX' - CONTINUE?
(Y)/N:y

L34 ANSWER 12 OF 14 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003338424 EMBASE
TITLE: Production of D-amino acids by N-acyl-D-amino acid amidohydrolase and its structure and function.
AUTHOR: Wakayama M.; Yoshimune K.; Hirose Y.; Moriguchi M.
CORPORATE SOURCE: M. Moriguchi, Department of Applied Chemistry, Faculty of Engineering, Oita University, Dannoharu 700, Oita 870-1192, Japan. mmorigu@cc.oita-u.ac.jp
SOURCE: Journal of Molecular Catalysis B: Enzymatic, (1 Sep 2003) 23/2-6 (71-85).
Refs: 59
ISSN: 1381-1177 CODEN: JMCEF8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB D-Amino acids have been widely used as synthetic materials for various compounds such as pharmaceuticals and agrochemicals. The manufacture of D-amino acids by fermentation is difficult, and enzymatic methods are mainly employed. At present, the optical resolution method using N-acyl-D-amino acid amidohydrolase is the most useful and convenient. In this review, the application of N-acyl-D-amino acid amidohydrolase to the production of D-amino acids and recent progress in the study of structure-function relationships from the standpoint of improving this enzyme for industrial application are discussed. .COPYRGT. 2003 Elsevier B.V. All rights reserved.

=> d hit 12

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(Y)/N:y

L34 ANSWER 12 OF 14 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
CT Medical Descriptors:
enzyme structure
protein function
fermentation
methodology
structure activity relation
industry
antibacterial activity
schizophrenia: DT, drug therapy
dementia: DT, drug therapy
amino acid sequence
deacylation
catalysis
bacterium
prediction
enzyme active site
human
nonhuman
review
Drug Descriptors:
*dextro amino acid: DV, drug development
*dextro amino acid: DT, drug therapy
*dextro amino acid: PR, pharmaceutics
*dextro amino acid: PD, pharmacology
*n acyl dextro amino acid amidohydrolase
*amidase
bacitracin
mycobacillin
dextro aspartic acid: EC, endogenous compound
dextro glutamic acid
dextro cysteine
malformin B1a
dextro leucine
circulin
dextro phenylalanine
fungisporin
gramicidin
polymyxin
tyrocidine
dextro valine
dactinomycin
valinomycin
dermorphin
dextro alanine
dextro serine: EC, endogenous compound
cycloserine: DT, drug therapy
cycloserine: PD, pharmacology
antiinfective agent
gramicidin A
aminoacylase
nateglinide
indinavir
omapatrilat

unindexed drug
unclassified drug

=> d iall abeq tech abex 13-14
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, EMBASE, WPIX' - CONTINUE?
(Y)/N:y

L34 ANSWER 13 OF 14 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-312940 [26] WPIX
DOC. NO. CPI: C1999-092380
TITLE: Linear and cyclic histogranin-derived peptides useful for treating chronic pain.
DERWENT CLASS: B02 B03 B04
INVENTOR(S): LEMAIRE, S
PATENT ASSIGNEE(S): (UYOT-N) UNIV OTTAWA; (LEMA-I) LEMAIRE S
COUNTRY COUNT: 84
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9921877	A1	19990506	(199926)*	EN	44	C07K007-08
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW						
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW						
AU 9897311	A	19990517	(199939)			C07K007-08
CA 2219437	A1	19990424	(199940)	EN		C07K005-103
CA 2224066	A1	19990424	(199940)	EN		C07K007-08
EP 1025119	A1	20000809	(200039)	EN		C07K007-08
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
US 6566327	B1	20030520	(200336)			A61K038-04<--
US 2004006013	A1	20040108	(200404)			A61K038-00<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9921877	A1	WO 1998-CA1002	19981026
AU 9897311	A	AU 1998-97311	19981026
CA 2219437	A1	CA 1997-2219437	19971024
CA 2224066	A1	CA 1998-2224066	19980224
EP 1025119	A1	EP 1998-951127	19981026
		WO 1998-CA1002	19981026
US 6566327	B1	WO 1998-CA1002	19981026
		US 2000-530123	20000706
US 2004006013	A1 Div ex	WO 1998-CA1002	19981026
	Div ex	US 2000-530123	20000706
		US 2003-437435	20030514

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9897311	A Based on	WO 9921877
EP 1025119	A1 Based on	WO 9921877

US 6566327 B1 Based on WO 9921877
US 2004006013 A1 Div ex US 6566327

PRIORITY APPLN. INFO: CA 1998-2224066 19980224; CA 1997-2219437 19971024
INT. PATENT CLASSIF.:
MAIN: **A61K038-00**; **A61K038-04**; C07K005-103; C07K007-08
SECONDARY: A61K031-195; A61K031-22; A61K031-395; **A61K038-07**; **A61K038-10**; **A61K038-12**; C07C237-22; **C07C279-14**; C07C327-42; C07D257-02; C07K005-04; C07K005-10; C07K005-11; **C07K005-12**; C07K007-06; C07K007-64

BASIC ABSTRACT:

WO 9921877 A UPAB: 19990707

NOVELTY - Linear or cyclic (pseudo)peptides (A) related to histogranin, are new.

DETAILED DESCRIPTION - (A) are of formulae (I) and (II), or their salts, esters and pseudopeptide analogs with one or more carbonyl in a peptide link replaced by thiocarbonyl or methylene and/or with one or more amide bonds replaced by the retro-verso form NH-CO.

R1 = Ra or (CH2)n-Rb;

Ra = hydrogen, alkyl, alkenyl or alkynyl;

Rb = amino, guanidino or imidazol-4-yl;

n = 0-10;

R2 = (CH2)n-CONH2;

R3 = Ra or (CH2)n-Rc;

Rc = phenyl, substituted by R11, R12 and R13, or indol-3-yl, substituted on the phenyl ring by R11, R12 and R13;

R11, R12 and R13 = same or different Ra, iodo, fluoro, bromo, chloro or hydroxy;

R4 = (CH2)n-Rb;

R5 and R9 = Ra, alkylcarbonyl, aminocarbonyl (optionally substituted by 1 or 2 alkyl), dialkylamino or (CH2)n-aryl;

R6, R7 and R8 = Ra;

R10 = Hydroxy, alkoxy, alkoxy, alkenyloxy, alkynloxy, amino alkylamino, dialkylamino, alkylaryl, arylalkoxy, aryloxy, alkoxyaryl, amino (optionally substituted by 1 or 2 alkyl), A1, A1-A2. A1-A2-A3, A1-A2-A3-A4 or A1-A2-A3-A4-A5;

A1 = Thr or Ser;

A2 = Leu, Gly, Ala, Val or Ile;

A3 = Tyr, Phe or Trp;

A4 = Gly, Ala, Leu, Ile or Val;

A5 = Phe, Tyr or Trp;

X = amino acid, A1, A1-A2, A1-A2-A3, A1-A2-A3-A4 or A1-A2-A3-A4-A5, and in this case A groups are as above or also a divalent group of formula (I)

with R1-R8 as above

ACTIVITY - Analgesic.

The peptide Gly-Gln-Ala-Arg had mean 50% effective dose in the mouse acetic acid writhing test of 3.9 nmole/mouse compared to 22.3 nmole/mouse for histogranin itself.

MECHANISM OF ACTION - (A) are antagonists of the N-methyl-D-asparatate receptor and also suppress production of prostaglandin E2 by macrophages.

USE - (A) are used to treat pain, especially chronic pain.

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B14-C01
TECH UPTX: 19990707

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred peptides: These are of formulae (III) or (IV):
Q1 = Gly, Ala, Val, Leu, Ile, Lys, His or Arg;
Q2 = Asp, L- or D-Gln;
Q3 = Gly, Ala, Val, Leu, Ile, Phe, Trp or Tyr;
Q4 = Lys, His, L- or D-Arg
or their pseudopeptides, salts or esters.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: All (A) are made by standard methods of solid-phase (psuedo)peptide synthesis.

ABEX UPTX: 19990707

SPECIFIC COMPOUNDS - Fifteen (A) are claimed, e.g. Gly-Gln-Gly-Arg; Gly-Gln-Ala-Arg or Gly-Gln-Tyr-Arg, and their cyclic forms, but most preferably cyclic forms of Gly-Gln-Tyr-D-Arg and Gly-D-Gln-Tyr-D-Arg.

ADMINSTRATION - (A) are administered orally, nasally, topically, by injection etc. A typical daily dose is 5-50 mg.

L34 ANSWER 14 OF 14 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-338498 [29] WPIX
DOC. NO. CPI: C2000-145421
TITLE: New imidazolidine derivatives useful for treating e.g. arthritis, inflammation, asthma, diabetes and tumors.
DERWENT CLASS: B02 B03
INVENTOR(S): SCHMIDT, W; SEIFFGE, D; STILZ, H U; WEHNER, V; SELFFGE, D
PATENT ASSIGNEE(S): (HMRI) HOECHST MARION ROUSSEL DEUT GMBH; (AVET) AVENTIS PHARMA DEUT GMBH; (SCHM-I) SCHMIDT W; (SEIF-I) SEIFFGE D; (STIL-I) STILZ H U; (WEHN-I) WEHNER V
COUNTRY COUNT: 39
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
CZ 9803726	A3	19990616	(199929)*			C07K005-097
NO 9805368	A	19990520	(199930)			C07D233-72
SK 9801580	A3	19990611	(199930)			C07D233-04
AU 9892421	A	19990610	(199934)			C07K005-12<--
DE 19751251	A1	19990520	(199934)			C07D233-76
ZA 9810543	A	19990728	(199935)		187	C07D000-00
CA 2254420	A1	19990519	(199945)	EN		C07D233-72
HU 9802653	A2	19990928	(199946)			C07D233-72
JP 11246531	A	19990914	(199948)		87	C07D233-72
CN 1225360	A	19990811	(199950)			C07D233-74
KR 99045365	A	19990625	(200036)			C07D233-72
NZ 332855	A	20000623	(200038)			C07K005-087
EP 918059	A1	19990526	(200043)B	GE	116	C07K005-097
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
MX 9809658	A1	19990601	(200058)			C07D233-72
BR 9804695	A	20010522	(200132)			C07D233-66
US 6331552	B1	20011218	(200205)			A61K031-415
US 2002143043	A1	20021003	(200267)			A61K031-4166
US 6521654	B2	20030218	(200317)			A61K031-4166
AU 755893	B	20030102	(200319)			C07K005-12<--
EP 918059	B1	20030625	(200349)	GE		C07K005-097
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU NL PT RO SE SI						
DE 59808804	G	20030731	(200353)			C07K005-097
ES 2202718	T3	20040401	(200425)			C07K005-097
MX 219609	B	20040330	(200474)			C07D233-72

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
CZ 9803726	A3		CZ 1998-3726	19981117
NO 9805368	A		NO 1998-5368	19981118
SK 9801580	A3		SK 1998-1580	19981117
AU 9892421	A		AU 1998-92421	19981118
DE 19751251	A1		DE 1997-1051251	19971119
ZA 9810543	A		ZA 1998-10543	19981118
CA 2254420	A1		CA 1998-2254420	19981117
HU 9802653	A2		HU 1998-2653	19981117
JP 11246531	A		JP 1998-328502	19981118
CN 1225360	A		CN 1998-122519	19981119
KR 99045365	A		KR 1998-49376	19981118
NZ 332855	A		NZ 1998-332855	19981117
EP 918059	A1		EP 1998-121670	19981113
MX 9809658	A1		MX 1998-9658	19981118
BR 9804695	A		BR 1998-4695	19981118
US 6331552	B1	Cont of	US 1998-195440	19981118
			US 2000-516587	20000301
US 2002143043	A1	Cont of	US 1998-195440	19981118
		Div ex	US 2000-516587	20000301
			US 2001-952028	20010914
US 6521654	B2	Cont of	US 1998-195440	19981118
		Div ex	US 2000-516587	20000301
			US 2001-952028	20010914
AU 755893	B		AU 1998-92421	19981118
EP 918059	B1		EP 1998-121670	19981113
DE 59808804	G		DE 1998-508804	19981113
			EP 1998-121670	19981113
ES 2202718	T3		EP 1998-121670	19981113
MX 219609	B		MX 1998-9658	19981118

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6521654	B2	Div ex	US 6331552
AU 755893	B	Previous Publ.	AU 9892421
DE 59808804	G	Based on	EP 918059
ES 2202718	T3	Based on	EP 918059

PRIORITY APPLN. INFO: DE 1997-19751251 19971119

INT. PATENT CLASSIF.:

MAIN: A61K031-415; A61K031-4166; C07D000-00; C07D233-04; C07D233-66; C07D233-72; C07D233-74; C07D233-76; C07K005-087; C07K005-097; **C07K005-12**

SECONDARY: A61K031-00; A61K031-41; A61K031-4178; A61K031-435; A61K031-44; A61K031-495; A61K031-535; A61K031-54; A61K031-55; A61K031-675; **A61K038-05**; **A61K038-06**; **A61K038-07**; A61P019-02; A61P025-28; A61P029-00; A61P037-00; A61P037-08; C07D233-22; C07D233-30; C07D233-54; C07D233-78; C07D233-96; **C07D235-02**; C07D401-06; C07D401-12; C07D403-00; C07D403-12; C07D405-12; C07D405-14; C07D407-12; C07D409-12; C07D413-04; C07D417-04; C07D487-10; C07D513-10; C07F009-6506; C07F009-6558; C07K005-023; C07K005-06; C07K005-065; C07K005-072; C07K005-075; C07K005-078; C07K005-08; C07K005-093;

C07K005-107; C07K005-117
EQUIVALENT ABSTRACT TREATED AS BASIC:
EP 918059 A UPAB: 20000907
NOVELTY - Imidazolidine derivatives (I) are new.
DETAILED DESCRIPTION - Imidazolidine derivatives of formula (I) are new.
W = R1-A-C(R13), R1-A-C(R13)=C or a group (i) or (ii), whose ring systems may contain one or two independent N, O or S heteroatoms and may optionally be mono- or polyunsaturated and/or be substituted by one or more independent R13 groups or by 1 or 2 double-bonded O and/or S atoms;
L = C(R13) or N;
m1, m2 = 0-6 (provided that m1 + m2 = 1-6);
Y = CO, C(=S) or CH2;
A = a direct bond, 1-6C alkylene, 3-7C cycloalkylene, phenylene, phenylene-(1-6C alkyl), phenylene-(2-6C alkenyl) or a 5- or 6-membered optionally substituted heterocycle, provided that the phenylenealkyl and phenylenealkenyl groups are bound to R1 via the aromatic ring;
B = 1-6C alkylene, 2-6C alkenylene, phenylene, phenylene-(1-3C alkyl), (1-3C alkylene)-phenyl or (1-3C alkylene)-phenyl-(1-3C alkyl), where the 1-6C alkylene and 2-6C alkenylene groups are optionally substituted;
E = tetrazolyl, (R8O)2P(O), R10OSO2, R9NHSO2, R6CO, R7CO, R10CO, CHO, R8O-CH2, R8CO-OCH2, R8aO-CO-O-CH2 or (R8O)2P(O)-O-CH2;
R = H, 1-8C alkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-1-8C alkyl, 6-14C aryl, 6-14C aryl-1-8C alkyl, heteroaryl or heteroaryl-1-8C alkyl (all aryl being optionally substituted);
R1 = H, 1-10C alkyl or fluoroalkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), R21-(6-14C aryl), R21-(6-14C aryl)-(1-8C alkyl), Het, Het-(1-8C alkyl) or X-NH-C(=NH)R20, X1-NH-R20, R21-O-R20, R21N(R21)-R20, R21-CO, R21-O-CO, R22N(R21)CO, R2CO-N(R21), R21O-N=, O= or S=;
X = H, 1-6C alkyl, (1-6C alkyl)carbonyl, (1-6C alkoxy)carbonyl, (1-10C alkyl)carbonyloxy-(1-6C alkoxy)carbonyl, optionally substituted 6-14C arylcarbonyl or aryloxycarbonyl, (6-14C aryl)-(1-6C alkoxy)carbonyl, CN, OH, 1-6C alkoxy, (6-14C aryl)-(1-6C alkoxy) or amino;
X1 = as for X or is R'-NH-C(=N-R'');
R', R'' = as for X;
R2 = H, 1-8C alkyl, optionally substituted 6-14C aryl or (6-14C aryl)-(1-8C alkyl) or 3-8C cycloalkyl;
R3 = e.g. H, 1-10C alkyl or fluoroalkyl, optionally substituted 6-14C aryl, 6-14C aryl-(1-8C alkyl), heteroaryl or heteroaryl-(1-8C alkyl), R11NH, CON(CH3)R4, CONHR4, COOR21, COOR15, CON(CH3)R15 or CONHR15;
R4 = H or optionally substituted 1-10C alkyl;
R5 = 6-14C aryl or 6-14C aryl-1-8C alkyl (both being optionally aryl substituted) or mono-or bicyclic 5-12 membered heterocyclic
R6 = an amino or imino acid, an optionally alkylated or arylalkylated azaamino acid or a di-, tri- or tetrapeptide which may be esterified, amidated or protected;
R7 = an N-bound 5-10 membered saturated mono- or polycyclic heterocycle which is optionally substituted;
R8 = H, 1-10C alkyl, or optionally substituted 6-14C aryl or 6-14C aryl-(1-8C alkyl);
R8a = as for R8, but is not H;
R9 = H, aminocarbonyl, (1-10C alkyl)aminocarbonyl or (3-8C cycloalkyl)aminocarbonyl;
R10 = e.g. OH, 1-10C alkoxy, 6-14C aryl-(1-8C alkoxy) or 6-14C aryloxy, or (R8)2NCO-(1-6C alkoxy)(the aryl groups in R10 may all be substituted);
R11 = H, R12a, R12aCO, CHO, R12a-OCO, R12b-CO, R12b-C(=S), R12a-SO2 or R12b- SO2;

R12a = 1-10C alkyl, 2-8C alkenyl, 2-8C alkynyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-14C aryl, 6-14C aryl-(1-8C alkyl), heteroaryl or heteroaryl-(1-8C alkyl), where the aromatic groups are optionally substituted;

R12b = NH2, di(1-10C alkyl)amino or R12a-NH;

R13 = H, 1-6C alkyl or fluoroalkyl, 6-14C aryl, 6-14C aryl-(1-6C alkyl), 3-8C cycloalkyl or 3-8C cycloalkyl-(1-6C alkyl), where the aromatic groups are optionally substituted;

R15 = R16-(1-6C alkyl) or R16;

R16 = 6-24 membered bi- or tricyclic group containing up to 4 N, O or S heteroatoms which is optionally substituted by 1-4C alkyl or oxo;

R21 = H, 1-8C alkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-14C aryl, 6-14C aryl-(1-8C alkyl), Het or Het-(1-8C alkyl), where the alkyl groups are optionally fluorinated and the aryl groups are optionally substituted;

R22 = R21, R21O, R21N(R21), R21CO, R21O-CO, R21N(R21)-CO, R21N(R21)-C(=N(R21)) or R21-CO-N(R21);

R30 = e.g. R32(R)N-CO-N(R)-R31, R32(R)N-C(=S)-N(R)-R31, R32-S(O)n-R31 or R12a-OCO-N(R)-R31;

provided that R30 is not R32-CO-R31 when W = R1-A-C(R13), A is a direct bond and R1 and R13 are H;

R31 = R33-R34-R35-R36, where the R36 is bound to the imidazolyl group on (I);

R32 = H, 1-8C alkyl or fluoroalkyl, 2-8C alkenyl, 2-8C alkynyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-12C bicycloalkyl, 6-12C bicycloalkyl-(1-8C alkyl), 6-12C tricycloalkyl, 6-12C tricycloalkyl-(1-8C alkyl), 6-14C aryl, heteroaryl or heteroaryl-(1-8C alkyl), where the aryl and heteroaryl groups are optionally substituted;

R20, R33 = a direct bond or 1-6C alkylene;

R34 = 1-8C alkylene, 3-12C cycloalkylene, 6-12C bicycloalkylene, 6-12C tricycloalkylene, or optionally substituted 6-14C arylene or heteroarylene;

R35 = a direct bond or 1-8C alkylene;

R36 = a direct bond, CO or S(O)n;

Het = 4-14 membered mono- or polycyclic aromatic or non-aromatic ring which contains 1-4 N, S or O heteroatoms and is optionally substituted;

e,h = 0 or 1;

n = 1 or 2.

A full set of definitions is given in the DEFINITIONS (Full Definitions) field.

An INDEPENDENT CLAIM is also included for preparation of (I).

ACTIVITY - Antiarthritic; antirheumatic; antiinflammatory; dermatological; immunosuppressive; neuroprotective; antiallergic; antiarteriosclerotic; vasotropic; antidiabetic; cytostatic; antiprotozoal.

((RS)-2-((RS)-4-phenyl-3-(4-(3-phenylureido)benzyl)-4-methyl-2,5-dioxoimidazolidin-1-yl)-2-(2-methylpropyl)acetyl)-L-aspartyl-L-phenylglycine (Ia) had an IC50 of 4 nM as an inhibitor of U397/VCAM-1 cell adhesion.

MECHANISM OF ACTION - Leukocyte migration inhibitor; VLA-4 inhibitor; antimetastatic.

USE - (I) are useful as leukocyte migration/adhesion inhibitors and VLA-4 inhibitors for treatment and prevention of arthritis, rheumatoid arthritis, polyarthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, inflammation of the central nervous system, asthma, allergy, cardiovascular disorders, arteriosclerosis, restenosis, diabetes, transplant rejection, immune and autoimmune disorders, tumors and tumor metastasis and malaria (all claimed). The compounds may also be used in diagnosis or in biochemical testing, and as intermediates for other pharmaceuticals.

Dwg.0/0

BASIC ABSTRACT:

CZ 9803726 A UPAB: 20000913

NOVELTY - Imidazolidine derivatives (I) are new.

DETAILED DESCRIPTION - Imidazolidine derivatives of formula (I) are new.

W = R1-A-C(R13), R1-A-C(R13)=C or a group (i) or (ii), whose ring systems may contain one or two independent N, O or S heteroatoms and may optionally be mono- or polyunsaturated and/or be substituted by one or more independent R13 groups or by 1 or 2 double-bonded O and/or S atoms;

L = C(R13) or N;

m1, m2 = 0-6 (provided that m1 + m2 = 1-6);

Y = CO, C(=S) or CH2;

A = a direct bond, 1-6C alkylene, 3-7C cycloalkylene, phenylene, phenylene-(1-6C alkyl), phenylene-(2-6C alkenyl) or a 5- or 6-membered optionally substituted heterocycle, provided that the phenylenealkyl and phenylenealkenyl groups are bound to R1 via the aromatic ring;

B = 1-6C alkylene, 2-6C alkenylene, phenylene, phenylene-(1-3C alkyl), (1-3C alkylene)-phenyl or (1-3C alkylene)-phenyl-(1-3C alkyl), where the 1-6C alkylene and 2-6C alkenylene groups are optionally substituted;

E = tetrazolyl, (R8O)2P(O), R10OSO2, R9NHSO2, R6CO, R7CO, R10CO, CHO, R8O-CH2, R8CO-OCH2, R8aO-CO-O-CH2 or (R8O)2P(O)-O-CH2;

R = H, 1-8C alkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-1-8C alkyl, 6-14C aryl, 6-14C aryl-1-8C alkyl, heteroaryl or heteroaryl-1-8C alkyl (all aryl being optionally substituted);

R1 = H, 1-10C alkyl or fluoroalkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), R21-(6-14C aryl), R21-(6-14C aryl)-(1-8C alkyl), Het, Het-(1-8C alkyl) or X-NH-C(=NH)R20, X1-NH-R20, R21-O-R20, R21N(R21)-R20, R21-CO, R21-O-CO, R22N(R21)CO, R2CO-N(R21), R21O-N=, O= or S=;

X = H, 1-6C alkyl, (1-6C alkyl)carbonyl, (1-6C alkoxy)carbonyl, (1-10C alkyl)carbonyloxy-(1-6C alkoxy)carbonyl, optionally substituted 6-14C arylcarbonyl or aryloxycarbonyl, (6-14C aryl)-(1-6C alkoxy)carbonyl, CN, OH, 1-6C alkoxy, (6-14C aryl)-(1-6C alkoxy) or amino;

X1 = as for X or is R'-NH-C(=N-R'');

R', R'' = as for X;

R2 = H, 1-8C alkyl, optionally substituted 6-14C aryl or (6-14C aryl)-(1-8C alkyl) or 3-8C cycloalkyl;

R3 = e.g. H, 1-10C alkyl or fluoroalkyl, optionally substituted 6-14C aryl, 6-14C aryl-(1-8C alkyl), heteroaryl or heteroaryl-(1-8C alkyl), R11NH, CON(CH3)R4, CONHR4, COOR21, COOR15, CON(CH3)R15 or CONHR15;

R4 = H or optionally substituted 1-10C alkyl;

R5 = 6-14C aryl or 6-14C aryl-1-8C alkyl (both being optionally aryl substituted) or mono-or bicyclic 5-12 membered heterocyclic

R6 = an amino or imino acid, an optionally alkylated or arylalkylated azaamino acid or a di-, tri- or tetrapeptide which may be esterified, amidated or protected;

R7 = an N-bound 5-10 membered saturated mono- or polycyclic heterocycle which is optionally substituted;

R8 = H, 1-10C alkyl, or optionally substituted 6-14C aryl or 6-14C aryl-(1-8C alkyl);

R8a = as for R8, but is not H;

R9 = H, aminocarbonyl, (1-10C alkyl)aminocarbonyl or (3-8C cycloalkyl)aminocarbonyl;

R10 = e.g. OH, 1-10C alkoxy, 6-14C aryl-(1-8C alkoxy) or 6-14C aryloxy, or (R8)2NCO-(1-6C alkoxy)(the aryl groups in R10 may all be substituted);

R11 = H, R12a, R12aCO, CHO, R12a-OCO, R12b-CO, R12b-C(=S), R12a-SO2 or R12b- SO2;

R12a = 1-10C alkyl, 2-8C alkenyl, 2-8C alkynyl, 3-12C cycloalkyl,

3-12C cycloalkyl-(1-8C alkyl), 6-14C aryl, 6-14C aryl-(1-8C alkyl), heteroaryl or heteroaryl-(1-8C alkyl), where the aromatic groups are optionally substituted;

R12b = NH2, di(1-10C alkyl)amino or R12a-NH;

R13 = H, 1-6C alkyl or fluoroalkyl, 6-14C aryl, 6-14C aryl-(1-6C alkyl), 3-8C cycloalkyl or 3-8C cycloalkyl-(1-6C alkyl), where the aromatic groups are optionally substituted;

R15 = R16-(1-6C alkyl) or R16;

R16 = 6-24 membered bi- or tricyclic group containing up to 4 N, O or S heteroatoms which is optionally substituted by 1-4C alkyl or oxo;

R21 = H, 1-8C alkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-14C aryl, 6-14C aryl-(1-8C alkyl), Het or Het-(1-8C alkyl), where the alkyl groups are optionally fluorinated and the aryl groups are optionally substituted;

R22 = R21, R21O, R21N(R21), R21CO, R21O-CO, R21N(R21)-CO, R21N(R21)-C(=N(R21)) or R21-CO-N(R21);

R30 = e.g. R32(R)N-CO-N(R)-R31, R32(R)N-C(=S)-N(R)-R31, R32-S(O)n-R31 or R12a-OCO-N(R)-R31;

provided that R30 is not R32-CO-R31 when W = R1-A-C(R13), A is a direct bond and R1 and R13 are H;

R31 = R33-R34-R35-R36, where the R36 is bound to the imidazolyl group on (I);

R32 = H, 1-8C alkyl or fluoroalkyl, 2-8C alkenyl, 2-8C alkynyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-12C bicycloalkyl, 6-12C bicycloalkyl-(1-8C alkyl), 6-12C tricycloalkyl, 6-12C tricycloalkyl-(1-8C alkyl), 6-14C aryl, heteroaryl or heteroaryl-(1-8C alkyl), where the aryl and heteroaryl groups are optionally substituted;

R20, R33 = a direct bond or 1-6C alkylene;

R34 = 1-8C alkylene, 3-12C cycloalkylene, 6-12C bicycloalkylene, 6-12C tricycloalkylene, or optionally substituted 6-14C arylene or heteroarylene;

R35 = a direct bond or 1-8C alkylene;

R36 = a direct bond, CO or S(O)n;

Het = 4-14 membered mono- or polycyclic aromatic or non-aromatic ring which contains 1-4 N, S or O heteroatoms and is optionally substituted;

e,h = 0 or 1;

n = 1 or 2.

A full set of definitions is given in the DEFINITIONS (Full Definitions) field.

An INDEPENDENT CLAIM is also included for preparation of (I).

ACTIVITY - Antiarthritic; antirheumatic; antiinflammatory; dermatological; immunosuppressive; neuroprotective; antiallergic; antiarteriosclerotic; vasotropic; antidiabetic; cytostatic; antiprotozoal.

((RS)-2-((RS)-4-phenyl-3-(4-(3-phenylureido)benzyl)-4-methyl-2,5-dioxoimidazolidin-1-yl)-2-(2-methylpropyl)acetyl)-L-aspartyl-L-phenylglycine (Ia) had an IC50 of 4 nM as an inhibitor of U397/VCAM-1 cell adhesion.

MECHANISM OF ACTION - Leukocyte migration inhibitor; VLA-4 inhibitor; antimetastatic.

USE - (I) are useful as leukocyte migration/adhesion inhibitors and VLA-4 inhibitors for treatment and prevention of arthritis, rheumatoid arthritis, polyarthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, inflammation of the central nervous system, asthma, allergy, cardiovascular disorders, arteriosclerosis, restenosis, diabetes, transplant rejection, immune and autoimmune disorders, tumors and tumor metastasis and malaria (all claimed). The compounds may also be used in diagnosis or in biochemical testing, and as intermediates for other pharmaceuticals.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B07-H; B12-K04; B14-A03B; B14-C03; B14-C09; B14-E10C; B14-F01; B14-F02; B14-F07; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-J05A; B14-K01A; B14-N17; B14-S04

ABEQ EP 918059 A UPAB: 20000907

NOVELTY - Imidazolidine derivatives (I) are new.

DETAILED DESCRIPTION - Imidazolidine derivatives of formula (I) are new.

W = R1-A-C(R13), R1-A-C(R13)=C or a group (i) or (ii), whose ring systems may contain one or two independent N, O or S heteroatoms and may optionally be mono- or polyunsaturated and/or be substituted by one or more independent R13 groups or by 1 or 2 double-bonded O and/or S atoms;

L = C(R13) or N;

m1, m2 = 0-6 (provided that m1 + m2 = 1-6);

Y = CO, C(=S) or CH2;

A = a direct bond, 1-6C alkylene, 3-7C cycloalkylene, phenylene, phenylene-(1-6C alkyl), phenylene-(2-6C alkenyl) or a 5- or 6-membered optionally substituted heterocycle, provided that the phenylenealkyl and phenylenealkenyl groups are bound to R1 via the aromatic ring;

B = 1-6C alkylene, 2-6C alkenylene, phenylene, phenylene-(1-3C alkyl), (1-3C alkylene)-phenyl or (1-3C alkylene)-phenyl-(1-3C alkyl), where the 1-6C alkylene and 2-6C alkenylene groups are optionally substituted;

E = tetrazolyl, (R8O)2P(O), R10OSO2, R9NHSO2, R6CO, R7CO, R10CO, CHO, R8O-CH2, R8CO-OCH2, R8aO-CO-O-CH2 or (R8O)2P(O)-O-CH2;

R = H, 1-8C alkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-1-8C alkyl, 6-14C aryl, 6-14C aryl-1-8C alkyl, heteroaryl or heteroaryl-1-8C alkyl (all aryl being optionally substituted);

R1 = H, 1-10C alkyl or fluoroalkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), R21-(6-14C aryl), R21-(6-14C aryl)-(1-8C alkyl), Het, Het-(1-8C alkyl) or X-NH-C(=NH)R20, X1-NH-R20, R21-O-R20, R21N(R21)-R20, R21-CO, R21-O-CO, R22N(R21)CO, R2CO-N(R21), R21O-N=, O= or S=;

X = H, 1-6C alkyl, (1-6C alkyl)carbonyl, (1-6C alkoxy)carbonyl, (1-10C alkyl)carbonyloxy-(1-6C alkoxy)carbonyl, optionally substituted 6-14C arylcarbonyl or aryloxycarbonyl, (6-14C aryl)-(1-6C alkoxy)carbonyl, CN, OH, 1-6C alkoxy, (6-14C aryl)-(1-6C alkoxy) or amino;

X1 = as for X or is R'-NH-C(=N-R'');

R', R'' = as for X;

R2 = H, 1-8C alkyl, optionally substituted 6-14C aryl or (6-14C aryl)-(1-8C alkyl) or 3-8C cycloalkyl;

R3 = e.g. H, 1-10C alkyl or fluoroalkyl, optionally substituted 6-14C aryl, 6-14C aryl-(1-8C alkyl), heteroaryl or heteroaryl-(1-8C alkyl), R11NH, CON(CH3)R4, CONHR4, COOR21, COOR15, CON(CH3)R15 or CONHR15;

R4 = H or optionally substituted 1-10C alkyl;

R5 = 6-14C aryl or 6-14C aryl-1-8C alkyl (both being optionally aryl substituted) or mono-or bicyclic 5-12 membered heterocyclic

R6 = an amino or imino acid, an optionally alkylated or arylalkylated azaamino acid or a di-, tri- or tetrapeptide which may be esterified, amidated or protected;

R7 = an N-bound 5-10 membered saturated mono- or polycyclic heterocycle which is optionally substituted;

R8 = H, 1-10C alkyl, or optionally substituted 6-14C aryl or 6-14C aryl-(1-8C alkyl);

R8a = as for R8, but is not H;

R9 = H, aminocarbonyl, (1-10C alkyl)aminocarbonyl or (3-8C cycloalkyl)aminocarbonyl;

R10 = e.g. OH, 1-10C alkoxy, 6-14C aryl-(1-8C alkoxy) or 6-14C aryloxy, or (R8)2NCO-(1-6C alkoxy)(the aryl groups in R10 may all be

substituted);
R11 = H, R12a, R12aCO, CHO, R12a-OCO, R12b-CO, R12b-C(=S), R12a-SO2 or R12b- SO2;
R12a = 1-10C alkyl, 2-8C alkenyl, 2-8C alkynyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-14C aryl, 6-14C aryl-(1-8C alkyl), heteroaryl or heteroaryl-(1-8C alkyl), where the aromatic groups are optionally substituted;
R12b = NH2, di(1-10C alkyl)amino or R12a-NH;
R13 = H, 1-6C alkyl or fluoroalkyl, 6-14C aryl, 6-14C aryl-(1-6C alkyl), 3-8C cycloalkyl or 3-8C cycloalkyl-(1-6C alkyl), where the aromatic groups are optionally substituted;
R15 = R16-(1-6C alkyl) or R16;
R16 = 6-24 membered bi- or tricyclic group containing up to 4 N, O or S heteroatoms which is optionally substituted by 1-4C alkyl or oxo;
R21 = H, 1-8C alkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-14C aryl, 6-14C aryl-(1-8C alkyl), Het or Het-(1-8C alkyl), where the alkyl groups are optionally fluorinated and the aryl groups are optionally substituted;
R22 = R21, R21O, R21N(R21), R21CO, R21O-CO, R21N(R21)-CO, R21N(R21)-C(=N(R21)) or R21-CO-N(R21);
R30 = e.g. R32(R)N-CO-N(R)-R31, R32(R)N-C(=S)-N(R)-R31, R32-S(O)n-R31 or R12a-OCO-N(R)-R31;
provided that R30 is not R32-CO-R31 when W = R1-A-C(R13), A is a direct bond and R1 and R13 are H;
R31 = R33-R34-R35-R36, where the R36 is bound to the imidazolyl group on (I);
R32 = H, 1-8C alkyl or fluoroalkyl, 2-8C alkenyl, 2-8C alkynyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-12C bicycloalkyl, 6-12C bicycloalkyl-(1-8C alkyl), 6-12C tricycloalkyl, 6-12C tricycloalkyl-(1-8C alkyl), 6-14C aryl, heteroaryl or heteroaryl-(1-8C alkyl), where the aryl and heteroaryl groups are optionally substituted;
R20, R33 = a direct bond or 1-6C alkylene;
R34 = 1-8C alkylene, 3-12C cycloalkylene, 6-12C bicycloalkylene, 6-12C tricycloalkylene, or optionally substituted 6-14C arylene or heteroarylene;
R35 = a direct bond or 1-8C alkylene;
R36 = a direct bond, CO or S(O)n;
Het = 4-14 membered mono- or polycyclic aromatic or non-aromatic ring which contains 1-4 N, S or O heteroatoms and is optionally substituted;
e,h = 0 or 1;
n = 1 or 2.

A full set of definitions is given in the DEFINITIONS (Full Definitions) field.

An INDEPENDENT CLAIM is also included for preparation of (I).

ACTIVITY - Antiarthritic; antirheumatic; antiinflammatory; dermatological; immunosuppressive; neuroprotective; antiallergic; antiarteriosclerotic; vasotropic; antidiabetic; cytostatic; antiprotozoal.

((RS)-2-((RS)-4-phenyl-3-(4-(3-phenylureido)benzyl)-4-methyl-2,5-dioxoimidazolidin-1-yl)-2-(2-methylpropyl)acetyl)-L-aspartyl-L-phenylglycine (Ia) had an IC50 of 4 nM as an inhibitor of U397/VCAM-1 cell adhesion.

MECHANISM OF ACTION - Leukocyte migration inhibitor; VLA-4 inhibitor; antimetastatic.

USE - (I) are useful as leukocyte migration/adhesion inhibitors and VLA-4 inhibitors for treatment and prevention of arthritis, rheumatoid arthritis, polyarthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, inflammation of the central nervous system, asthma, allergy, cardiovascular disorders, arteriosclerosis, restenosis, diabetes, transplant rejection, immune and autoimmune disorders, tumors and tumor metastasis and malaria (all claimed). The

compounds may also be used in diagnosis or in biochemical testing, and as intermediates for other pharmaceuticals.
Dwg.0/0

TECH UPTX: 20001114
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared by reacting compounds of formula (ii) and (iii) together.
G = COOH (1-6C alkoxy)carbonyl or activated carbonic acid (sic).

ABEX UPTX: 20001114
SPECIFIC COMPOUNDS - Over 220 compounds (I) are disclosed, e.g. -((RS)-2-((RS)-4-phenyl-3-(4-(3-phenylureido)benzyl)-4-methyl-2,5-dioxoimidazolidin-1-yl)-2-(2-methylpropyl)acetyl)-L-aspartyl-L-phenylglycine (Ia).

ADMINISTRATION - Daily oral dose is 0.01-100 (preferably 0.1-10, especially 0.3-2) mg/kg, while the daily intravenous dose is 0.01-50 (preferably 0.01-10) mg/kg. Administration may also be vaginal, rectal, topical, percutaneous, nasal or via other parenteral routes.
DEFINITIONS - Full Definitions:
W = R1-A-C(R13), R1-A-C(R13)=C or a group (i) or (ii), whose ring systems may contain one or two independent N, O or S heteroatoms and may optionally be mono- or polyunsaturated and/or be substituted by one or more independent R13 groups or by 1 or 2 double-bonded O and/or S atoms;
L = C(R13) or N;
m1, m2 = 0-6 (provided that m1 + m2 = 1-6);
Y = CO, C(=S) or CH2;
A = a direct bond, 1-6C alkylene, 3-7C cycloalkylene, phenylene, phenylene-(1-6C alkyl), phenylene-(2-6C alkenyl) or a 5- or 6-membered optionally substituted heterocycle, provided that the phenylenealkyl and phenylenealkenyl groups are bound to R1 via the aromatic ring;
B = 1-6C alkylene, 2-6C alkenylene, phenylene, phenylene-(1-3C alkyl), (1-3C alkylene)-phenyl or (1-3C alkylene)-phenyl-(1-3C alkyl), where the 1-6C alkylene and 2-6C alkenylene groups may be substituted by one or more 1-8C alkyl, 2-8C alkenyl, 3-10C cycloalkyl, 3-10C cycloalkyl-(1-6C alkyl), optionally substituted 6-14C aryl, 6-14C aryl-(1-6C alkyl) (whose aryl moiety is optionally substituted), optionally substituted heteroaryl, or heteroaryl-(1-6C alkyl) (whose heteroaryl group is optionally substituted);
E = tetrazolyl, (R8O)2P(O), R10OSO2, R9NHSO2, R6CO, R7CO, R10CO, CHO, R8O-CH2, R8CO-OCH2, R8aO-CO-O-CH2 or (R8O)2P(O)-O-CH2;
R = H, 1-8C alkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-1-8C alkyl, 6-14C aryl, 6-14C aryl-1-8C alkyl, heteroaryl or heteroaryl-1-8C alkyl (all aryl being optionally substituted);
R1 = H, 1-10C alkyl or fluoroalkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), R21-(6-14C aryl), R21-(6-14C aryl)-(1-8C alkyl), Het, Het-(1-8C alkyl) or X-NH-C(=NH)R20, X1-NH-R20, R21-O-R20, R21N(R21)-R20, R21-CO, R21-O-CO, R22N(R21)CO, R2CO-N(R21), R21O-N=, O= or S=;
X = H, 1-6C alkyl, (1-6C alkyl)carbonyl, (1-6C alkoxy)carbonyl, (1-10C alkyl)carbonyloxy-(1-6C alkoxy)carbonyl, optionally substituted 6-14C arylcarbonyl or aryloxycarbonyl, (6-14C aryl)-(1-6C alkoxy)carbonyl, CN, OH, 1-6C alkoxy, (6-14C aryl)-(1-6C alkoxy) or amino;
X1 = as for X or is R'-NH-C(=N-R'');
R', R'' = as for X;
R2 = H, 1-8C alkyl, optionally substituted 6-14C aryl or (6-14C aryl)-(1-8C alkyl) or 3-8C cycloalkyl;
R3 = H, 1-10C alkyl or fluoroalkyl, optionally substituted 6-14C aryl, 6-14C aryl-(1-8C alkyl), heteroaryl or heteroaryl-(1-8C alkyl), 3-8C cycloalkyl, 3-8C cycloalkyl-(1-8C alkyl, 6-12C bicycloalkyl, 6-12C bicycloalkyl-(1-8C alkyl), 6-12C tricycloalkyl, 6-12C tricycloalkyl-(1-8C alkyl), 2-8C alkenyl, 2-8C alkynyl, R11NH, CON(CH3)R4, CONHR4, COOR21,

COOR15, CON(CH3)R15 or CONHR15;
R4 = H or optionally substituted 1-10C alkyl;
R5 = 6-14C aryl or 6-14C aryl-1-8C alkyl (both being optionally aryl substituted) or mono-or bicyclic 5-12 membered heterocyclic
R6 = an amino or imino acid, an optionally alkylated or arylalkylated azaamino acid or a di-, tri- or tetrapeptide which may be esterified, amidated or protected;
R7 = an N-bound 5-10 membered saturated mono- or polycyclic heterocycle which is optionally substituted;
R8 = H, 1-10C alkyl, or optionally substituted 6-14C aryl or 6-14C aryl-(1-8C alkyl);
R8a = as for R8, but is not H;
R9 = H, aminocarbonyl, (1-10C alkyl)aminocarbonyl, (3-8C cycloalkyl)aminocarbonyl, optionally substituted (6-14C aryl)aminocarbonyl, 1-10C alkyl, optionally substituted 6-14C aryl or 3-8C cycloalkyl;
R10 = OH, 1-10C alkoxy, 6-14C aryl-(1-8C alkoxy) or 6-14C aryloxy, (1-8C alkyl)carbonyloxy-(1-6C alkoxy), 6-14C arylcarbonyloxy-(1-6C alkoxy), (1-8C alkoxy)carbonyloxy-(1-6C alkoxy), 6-14C aryloxycarbonyloxy-(1-6C alkoxy), 6-14C aryl-(1-6C alkoxy)carbonyloxy-(1-6C alkoxy), NH2, mono- or di-(1-10C alkyl)amino or (R8)2NCO-(1-6C alkoxy)(the aryl groups in R10 may all be substituted);
R11 = H, R12a, R12aCO, CHO, R12a-OCO, R12b-CO, R12b-C(=S), R12a-SO2 or R12b- SO2;
R12a = 1-10C alkyl, 2-8C alkenyl, 2-8C alkynyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-14C aryl, 6-14C aryl-(1-8C alkyl), heteroaryl or heteroaryl-(1-8C alkyl), where the aromatic groups are optionally substituted;
R12b = NH2, di(1-10C alkyl)amino or R12a-NH;
R13 = H, 1-6C alkyl or fluoroalkyl, 6-14C aryl, 6-14C aryl-(1-6C alkyl), 3-8C cycloalkyl or 3-8C cycloalkyl-(1-6C alkyl), where the aromatic groups are optionally substituted;
R15 = R16-(1-6C alkyl) or R16;
R16 = 6-24 membered bi- or tricyclic group containing up to 4 N, O or S heteroatoms which is optionally substituted by 1-4C alkyl or oxo;
R21 = H, 1-8C alkyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-14C aryl, 6-14C aryl-(1-8C alkyl), Het or Het-(1-8C alkyl), where the alkyl groups are optionally fluorinated and the aryl groups are optionally substituted;
R22 = R21, R21O, R21N(R21), R21CO, R21O-CO, R21N(R21)-CO, R21N(R21)-C(=N(R21)) or R21-CO-N(R21);
R30 = R32(R)N-CO-N(R)-R31, R32(R)N-C(=S)-N(R)-R31, R32(R)N-S(O)n-N(R)-R31, R32-CO-N(R)-R31, R32-C(=S)-N(R)-R31, R32-S(O)n-N(R)-R31, R32-N(RO-CO-R31, R32-N(RO-C(=S)-R31, R32-N(R)-S(O)n-R31, R3-CO-R31, R32-C(=S)-R31, R32-S(O)n-R31 or R12a-OCO-N(R)-R31;
provided that R30 is not R32-CO-R31 when W = R1-A-C(R13), A is a direct bond and R1 and R13 are H;
R31 = R33-R34-R35-R36, where the R36 is bound to the imidazolyl group on (I);
R32 = H, 1-8C alkyl or fluoroalkyl, 2-8C alkenyl, 2-8C alkynyl, 3-12C cycloalkyl, 3-12C cycloalkyl-(1-8C alkyl), 6-12C bicycloalkyl, 6-12C bicycloalkyl-(1-8C alkyl), 6-12C tricycloalkyl, 6-12C tricycloalkyl-(1-8C alkyl), 6-14C aryl, heteroaryl or heteroaryl-(1-8C alkyl), where the aryl and heteroaryl groups are optionally substituted;
R20, R33 = a direct bond or 1-6C alkylene;
R34 = 1-8C alkylene, 3-12C cycloalkylene, 6-12C bicycloalkylene, 6-12C tricycloalkylene, or optionally substituted 6-14C arylene or heteroarylene;
R35 = a direct bond or 1-8C alkylene;
R36 = a direct bond, CO or S(O)n;

Het = 4-14 membered mono- or polycyclic aromatic or non-aromatic ring which contains 1-4 N, S or O heteroatoms and is optionally substituted;
e,h = 0 or 1;
n = 1 or 2.

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